DISSERTATION ON

A STUDY ON PREVALENCE OF MICROALBUMINURIA IN RHEUMATOID ARTHRITIS AND ITS ASSOCIATION WITH DISEASE ACTIVITY

Dissertation Submitted To

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY,

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CHENNAI – 600032

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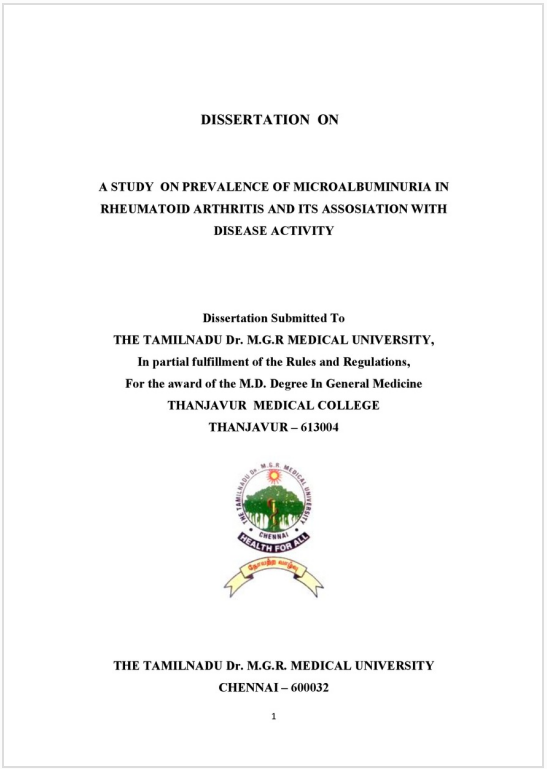

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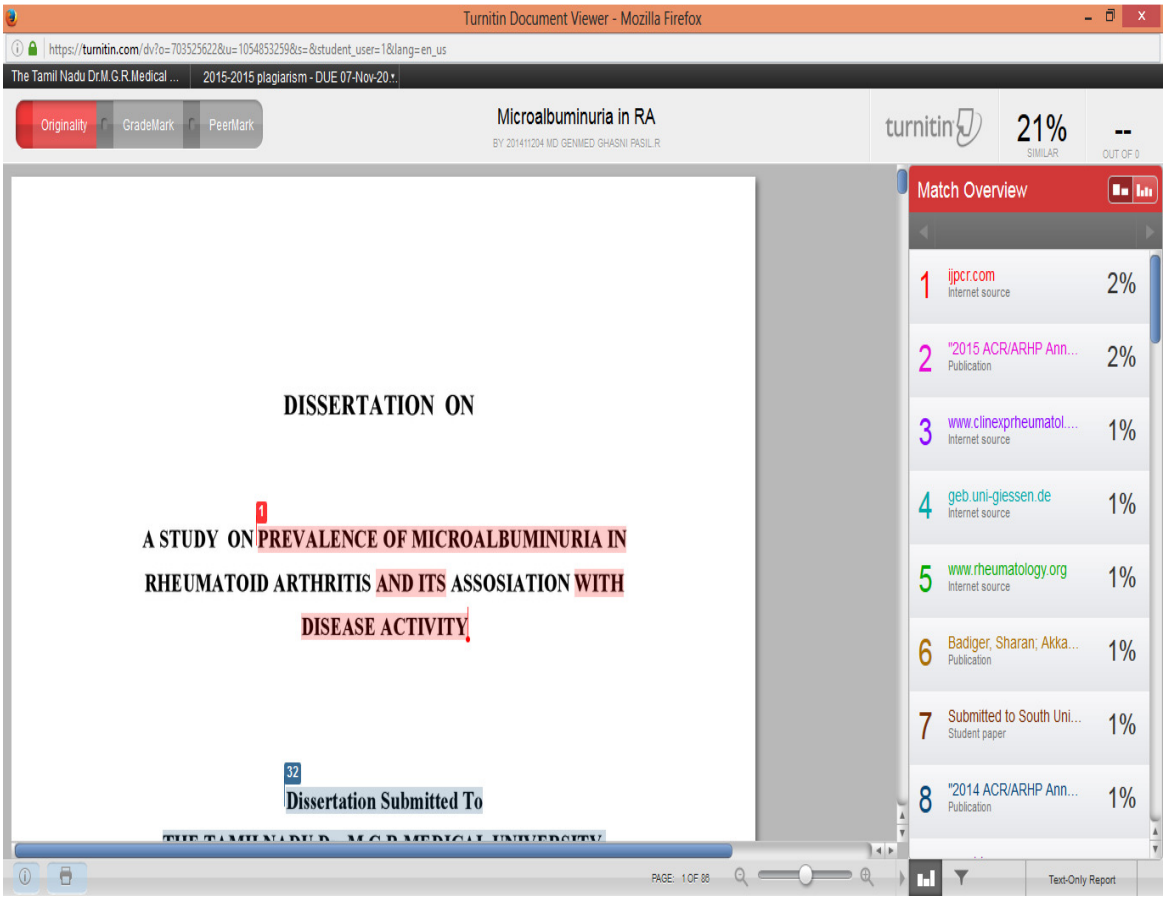
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LIST OF ABBREVIATIONS

- **ACR**-American College of Rheumatology
- **ADA**-American Diabetes Association
- **CRP**-C-Reactive Protein
- **DAS**-Disease Activity Score
- **DMARD**-Disease Modifying Anti Rheumatic Drugs
- **EAM**-Extra Articular Manifestations
- **ESR**-Erythrocyte Sedimentation Rate
- **EULAR**- EUropean League Against Rheumatism
- **IL**-Interleukin
- **MA**-MicroAlbuminuria
- **NSAID**-Non-Steroidal Anti-Inflammatory Drug
- **RA Factor**-Rheumatoid Factor
- **RA**-Rheumatoid Arthritis
- **RN**-Rheumatoid Nodules
- **SD**-Standard Deviation
- **TNF-α**-Tumor Necrosis Factor alpha
- **UACR**-Urine Albumin Creatinine Ratio
- **UAE**-Urine Albumin Excretion
- **WHO**-World Health Organization

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease characterised by symmetric peripheral polyarthritis, resulting in joint damage and physical disability. Its aetiology is unknown. It is the commonest form of chronic inflammatory arthritis. Being a systemic disease, it results in a wide variety of extraarticular manifestations, like fatigue, subcutaneous nodules, pulmonary involvement, pericarditis, peripheral neuropathy,vasculitis, and hematological abnormalities.[1]

Many reports in history describes a disease condition similar to Rheumatoid Arthritis, including those by Hippocrates[2], Greek physician Arataeus, Caesar's physician Scribonius, the Byzantine physician Soranus, Emperor Constantine IX's adviser Michael Psellus[345], and Charaka from India, and also translation from Latin by Short, of Sydenhams (1676)[6.] The first explanation of Rheumatoid Arthritis accepted by modern medicine was seen in the dissertation of Augustin JacobLandré-Beauvais from the year 1800. He described acute onset of polyarthritis in a 35 year old female, which slowly ceased , resulting in wrist and hands deformities, which recurred.[7]

Archibald Garrod coined the term Rheumatoid Arthritis in 1859.[8] But the term Rheumatoid Arthritis came into use in 1941.[9]

AIM AND OBJECTIVES

To know

1) The prevalence of microalbuminuria in patients having rheumatoid arthritis.

2) The relationship between microalbuminuria and disease activity in rheumatoid arthritis as assessed by parameters like DAS28 score,ESR,CRP,RA Factor and presence of active symptoms.

DIAGNOSIS

Diagnosis of Rheumatoid Arthritis is by the use of Modified American College of Rheumatology (ACR) criteria (1987)[10]

Modified ACR criteria-1987

CRITERION	DEFINITION
1.Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2.Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously having had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joint areas are right or left PIP, MCP,wrist, elbow, knee, ankle and MTP joints
3.Arthritis of hand joints	At least 1 joint area swollen (as described above) in PIP, MCP,or Wrist joint .
4.Symmetric arthritis	Simultaneous involvement of the same joint areas (as definedin 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is accepted without absolute symmetry)
5.Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces or in juxtaarticular regions, observed by a physician
6.Serum rheumatoid factor	Detection of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7.Radiolographicchanges	radiolographic changes typical of RA seen on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked near the involved joints (osteoarthritis changes alone do not qualify)

4 or more out of these 7 criteria is diagnostic of rheumatoid arthritis. Criteria 1 to 4 should be present for 6 weeks or more. Patients with 2 clinical diagnoses are not excluded.

This has a sensitivity of 92%, and specificity of 89.3%.

Generally, most of the serologic studies are neither sensitive nor specific for Rheumatoid Arthritis but anti-cyclic citrullinated peptide antibodies (anti-CCP antibodies) has more than 90% specificity.[11]

Rheumatoid Arthritis can start at any age, usually in the fourth decade of life. It is more commonly seen in females with female to male ratio – 3:1 and this excess is greater in young people and the age related incidence is almost equal in elderly people.[12]

Rheumatoid Arthritis is prevalent world wide involving all ethnic groups with 0.3-1% prevalence. In India the prevalence is around0.65-0.75%.[13] and in rural population it is 0.7% [14]

There are several extra-articular manifestations (EAM) in Rheumatoid Arthritis, one among them being renal involvement[15]. Renal impairment is highly prevalent as denoted by reduced glomerular filtration and tubularfunction[161718]. Many morphological findings in the kidneys have beendocumented[161920] and renal disease is thought to be a frequent cause of death in Rheumatoid Arthritis [21].So, identifying those at risk of developing clinical nephropathy is important and for this sensitive measure of renal function should be available.

Protein loss from glomerulus in Rheumatoid Arthritis is implicated to complications caused by the disease in its advance stages like

- direct injury to kidney caused by the disease, or
- the side effects causing nephrotoxic drugs,or
- both.

Subclinical renal dysfunction is also common in Rheumatoid Arthritis, and most of these can't be detected by routine lab tests like urine total protein assays or Albustix.[2223]

Microalbuminuria (MA) is found to be a sensitive indicator of subclinical renal dysfunction..American Diabetes Association (ADA) defines microalbuminuria as urinary albumin excretion of 30–299 mg/ 24 h or albumin/ creatinine ratio of 30-299μg albumin/mg creatinine[24].

The "Gold Standard" for estimating urine albumin quantitatively and defining Microalbuminuria, is 24-hour urine sample collection. But, it is cumbersome and error- prone .[2526]Currently, the National Kidney Foundation recommends detection of microalbuminuria with spot Urine Albumin-Creatinine Ratio (UACR) obtained under standardized conditions. Albumin-Creatinine Ratio (ACR) is more convenient for patients and less likely to get false results due to improper methods used for collecting the urine sample.[27]

Various methods are being used for measuring ACR. They are:

- ❖ Dipstick method.
- ❖ Semi quantitative methods
  - ✓ Chemical precipitation(Sulphosalicylic acid trichloroacetic acid)
  - ✓ Immune precipitation (Micral test)
- ❖ Photometric method
- ❖ Nephelometric method.
- ❖ Sensitive quantitative methods
  - ✓ Radioimmuno assay(gold standard)
  - ✓ Cellulose acetate agarose gel electrophoresis.

Calculations (formulae): Urine Albumin:creatinine ratio(UACR)

It is ratio of urinary albumin to urinary creatinine , usually expressed as milligram of albumin excreted per gram of urinary creatinine.

$$\textbf{ACR (mg/g)} = \frac{albumin(mg/dl)}{creatinine(mg/dl)} \textbf{x 1000.}$$

For many diseases including diabetes ,microalbuminuria is considered to be a significant marker of mortality[28].Numerous studies have shown association of microalbuminuria with increased risk for renal and cardiovascular mortality and morbidity in diabetes, hypertension , patient swith acute myocardial infarction and also in general population. Rheumatoid Arthritis patients with microalbuminuria were seen to have increased mortality with hazard ratio 2.77 when compared to those with normal clinical renal findings.[28]

Earlier presence of microalbuminuria may be an indicator of risk for renal dysfunction.Increased excretion of albumin in urine suggests not only glomerular disease, but also the disease activity and inflammatory state.[29]

Microalbuminuria is more prevalent in Rheumatoid Arthritis patients than in general population. For exact assessment of subclinical renal dysfunction in Rheumatoid Arthritis patients, estimation of microalbuminuria is a reliable method. Patients with Rheumatoid Arthritis are at increased risk of developing renal complications and presence of proteinuria increases the mortality rate. Therefore in clinical practice, it is essential to have a sensitive method for measuring renal dysfunction [303132]

With the invent of assays sensitive and specific for urinary albumin ,earlier detection of glomerular abnormalities has been made possible in patients without any renal involvement clinically[129]

Few of the parameters which were used for observing the disease activity in Rheumatoid Arthritis were ESR,CRP, etc. But there is individual variation in the presentation and course of RA. The clinical features of RA varies widely with complaints such as fatigue , weakness , arthralgias , joint stiffness, joint swelling , functional impairment of joints involved , low grade fever , weight loss and so on .

Since this disease has varied expression, a group of certain variables is being used for evaluating the severity of the disease,joint destruction and disabilities[3334]. The disease activity score (DAS) was developed, which is a more valid variable for measuring the Rheumatoid Arthritis disease activity when compared with the various existing disease activity variables[3536]. DAS28 is more valuable in doing researches.

Advantages of DAS

(i) It has a continuous scale with a Gaussian distribution. It indicates the extent of underlying inflammation. DAS has more information when compared to single measures alone, its values can be interpreted clinically, and is very sensitive to small effects.

(ii) It is also a component in EULAR response criteria which signifies a clinically important target of disease modifying anti-rheumatic drug (DMARD) therapy.

(iii) Since a measure with an absolute value is being incorporated, treatment responses in clinical trials can be meaningfully compared, especially in case of comparative or non-superiority trials.

(iv) It will be helpful in future trials of highly effective DMARDs.

(v) results of the trials conducted can be analysed as a clinically significant result that is applicable to a clinical set up. The disease activity score (DAS) can be helpful in monitoring the suppression of rheumatoid arthritis disease activity with DMARDs or "biologicals".

(vi) Measures like "time-to-low-disease activity" or "time-in-low-disease activity" possibly will become valid as endpoints in clinical trials as soon as even more efficient new drugs become available in the future; these potential endpoints can already be calculated by means of the DAS and DAS28.

Problems in calculation and interpretation are the major disadvantages of indices such as disease activity score (DAS).[37]

Since decreased and non-graded joint counts are employed in DAS28, it is easier to complete than DAS. The DAS28 has a continuous scale ranging between 0and 9.4, and it frequently exhibits a Gaussian distribution in patients with Rheumatoid Arthritis. Direct comparison of DAS andDAS28 values is not possible; however there exists a formula for converting DAS28 into DAS values.[38]

As per the ARA criteria, a disease activity score (DAS)< 2.6 denotes remission.[39]This means that almost all Rheumatoid Arthritis patients in remission have a DAS28 < 2.6, however not all patients with DAS28 < 2.6 are in remission. In a patient,a change of 1.2 (i.e., 2 times the measurement error) of the DAS28is thought to besignificant.[38]

DAS28 are measures with absolute values, they can be utilized to find out and assess the status and course of disease activity in individual RA patients, in distinction with relative measures such as the ACR improvement criteria.[4041]

The validation profile of DAS28 (ESR) and DAS28 (CRP) was alike. This suggests that both measures are helpful in assessing disease activity in patients with Rheumatoid Arthritis[42]. DAS28-CRP may possibly undervalue disease activity in Rheumatoid Arthritis patients, when compared with DAS28-ESR for both sexes and various age groups[4344]. There aren't many studies conducted to assess the relationship between microalbuminuria and Rheumatoid Arthritis disease activity according to DAS28 score, although DAS28has been widely validated and are frequently used in RA clinical trials.

The present study is conducted to estimate the prevalence of microalbuminuria in Rheumatoid Arthritis and its association with disease activity using Disease Activity Score 28(DAS28-ESR).

REVIEW OF LITERATURE

The aetiology of Rheumatoid Arthritis is not known. It involves interaction among genotype, various environmental triggers, and chance.

MacGregor AJ et al[45] implicated genetic factors in Rheumatoid Arthritis in their twin studies in 2000. They found the concordance rates to be 15 to 30% and 5%among monozygotic and dizygotic twins respectively.

Wellcome Trust Case Control Consortium[46], in 2007, conducted a Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. The study showed that immune regulatory factors trigger the disease.

Stastny P.[47] found that HLA-DR4is associated with Rheumatoid Arthritis and also that the relative risk of Rheumatoid Arthritis in patients with this allele is around 4-5.

Gregersen PK et al[48] in 1987, found that only some of the subtypes of HLA-DR4 (HLA-DW4 and HLA-DW14) are associated with Rheumatoid Arthritis; and **Auger I** et al [49] in 1997observed that shared epitope on the HLA molecule (HLADRB1) has high association with RA .**Aghighi Y** et al[50] in 2007 proposed and found that patients with EBV infection have increased risk of developing JRA. Association of Rheumatoid Arthritis with infectious agents like Epstein - Barr virus, Cytomegalo Virus, proteus species, and

Escherichia coli and their products(e.g., heat-shock proteins) may be attributed to some form of molecular mimicry though exact mechanism is unknown.[51]

Rheumatoid factor (RF) is a high-affinity autoantibody against the Fc part of immunoglobulin and its induction is triggered by immune complexes during infection. For a long time, Rheumatoid Factor was used as diagnostic marker of Rheumatoid Arthritis and its role in the pathogenesis of the disease has already been established.

In a study conducted by **Wegner N** et al[52]in 2010, with the use of immunoblotting technique they found that there appears to be an association of periodontal disease with RA: *Porphyromonas gingivalis*which expresses *PAD* (peptidyl arginine deaminases), is seen to be abletopromote citrullination of mammalian proteins. Deleting the bacterial PAD gene resulted in complete discontinuation of protein citrullination .Inactivating arginine gingipains resulted in decreased citrullination but not lysine gingipains.

It is now found that gut micro flora plays a role in the development of autoimmunity in articular models. There are specific, potentially traceable clinical bacterial signatures that are emerging in association with autoantibody positive Rheumatoid Arthritis.**Scher JU** et al[53]advocatedthat production of anti-citrullinated peptide antibodies (ACPA) may have association with greater populations of Prevotellaceae in both oral and

intestinal micro flora. They proposed that this altered micro flora may be responsible for the development of auto inflammatory disease in some predisposed individuals, by many mechanisms including cyclic citrullinated peptide generation or activating Th17cell in the intestinal mucosa. They also came to a conclusion that additional investigations would be helpful in finding out the oral and intestinal microbial flora as potential triggers for autoimmunity and clinical Rheumatoid Arthritis. It has been accepted that risk of Rheumatoid Arthritis is more in women than in men. There is a link between the hypothalamic–pituitary–adrenal axis and production of cytokine. In a study done by **Capellino S** et al[54], in 2010,it was observed that around the onset of Rheumatoid Arthritis ,local catecholamine-producing cells starts replacing sympathetic nerve fibres. These locally produced catecholamines when modulated have strong anti-inflammatory effects in vivo and in vitro. Severe life threatening morbidity associated with rheumatoid arthritis is being supported by the above given data.

Rheumatoid factor (RF) is an IgM antibody against the Fc segment of IgG antibody seen in about 70% of Rheumatoid Arthritis patients.[55] There is proof suggesting involvement of rheumatoid factor in the pathogenesis of Rheumatoid Arthritis[56]. **Silman AJ and Hockberg**[57,] in their study found that enhanced presentation of immune-complexed agents, cross-linkage and stabilization of low-avidity IgG antibodies, and cryoprecipitation are the mechanisms in pathogenesis of Rheumatoid Arthritis. **Rantapaa-Dahlqvist S**

et al[56],observed that autoantibodies like Rheumatoid Factor and anti-cyclic citrullinated peptide antibodies (anti-CCP antibodies), are frequently (not always) seen in patients before they develop arthritis (i.e, in the pre-articular phase of Rheumatoid Arthritis) and in some series ,levels of auto antibodies have elevated. They also observed existence of epitope spreading along with the disease onset and its progress .Rheumatoid Factor does not have diagnostic specificity in Rheumatoid Arthritis. It can be seen in a wide variety of conditions other than Rheumatoid Arthritis like bacterial infection, liver disease, lymphoproliferative disorders and other autoimmune disorders.

The occurrence of Rheumatoid Factor(not anti-CCP)in Rheumatoid Arthritis is related with extra articular manifestations and a milder form of the disease is seen when Rheumatoid Factor is not present.[585]

Turesson C et al[59] conducted a study on 35 consecutive patients with severe extra-articular manifestations (EAM) and comparing them with 70 patients having Rheumatoid Arthritis without extra articular manifestations, individually matched for age, sex and duration of the disease, served as controls. Rheumatoid Factor was positive in94% v 71% of patients and control population, respectively ($p = 0.006$), and levels of Rheumatoid Factor were more in patients with extra articular manifestations (median interquartile range (IQR) 245 IU/ml (94-604) v73 IU/ml (not detected-165); $p = 0.001$). They came to a conclusion that in Rheumatoid Arthritis patients, both Rheumatoid Factor and anti-CCPs are associated with severe extra articular

manifestations though much stronger association exists for Rheumatoid Factor. This is indicative of their function in the pathogenesis of extra articular manifestations.

Extra articular manifestations are commonly seen in about 17.8%–50.1% of patients with Rheumatoid Arthritis and are related with poorer outcomes than those without extra articular manifestations. They have higher morbidity and mortality, and poor functional status.[6263646566]

Calguneri M et al[62] from Turkey observed in their study on 526 patients that 202 patients had extra articular manifestations (with a frequency of 38.4%), most common among them being rheumatoid nodules (18.1%).Sjogrens syndrome symptoms, lung findings, livedo reticularis, Raynaud's phenomenon, carpal tunnel syndrome, vasculitis, amyloidosis, and Felty syndrome were present in 11.4%, 4.8%, 4.8%,3%, 2.8%, 1.3%, 1.1%, and 0.3%of the patients, respectively. In general, patients with positive Rheumatoid Factor presents with extra articular manifestations and rheumatoid nodule is more commonly than those in whom Rheumatoid Factor is negative. They also observed that rheumatoid nodules are more frequently seen in males.

Myasoedova etal[65] in 2011 gathered together from the available medical records, information on incident extra articular manifestations in Rheumatoid Arthritis patients among Olmsted County residents who first met the 1987ACR(American College of Rheumatology) criteria for Rheumatoid

Arthritis between January 1, 1995, and December 31, 2007. They were followed until demise, relocation from Olmsted County, or December 31, 2008. A predefined criteria was used to classify extra articular manifestations and compared to the corresponding 1985-1994 inception Rheumatoid Arthritis cohort (n = 147). They found that the 10-year cumulative incidence of any extra articular manifestations (50.1%) and severe extra articular manifestations (6.7%) in the 1995-2007 cohort was similar to the 1985-1994 cohort (46.2% and9.7%, respectively). The cumulative vasculitic incidence over the past ten years was significant but not other features of extra articular manifestations, was relatively lower in the 1995-2007 cohort (0.6%) when comparing with the 1985-1994 cohort (3.6%). Positive RF, erosive/destructive joints, and use of drugs like DMARDs and systemic steroids had significant association with extra articular manifestations in the 1995-2007 cohort.

The 1995-2007 cohort showed increased risk of mortality in association with extra articular manifestations (HR 2.1, 95% CI 1.2, 3.7). The reduction in mortality following extra articular manifestations in the 1995-2007 cohort opposed to the1985-1994 cohort did not attain statistical significance (HR 0.6, 95% CI 0.3, 1.2, p =0.16). They came to a conclusion that presence of extra articular manifestations in Rheumatoid Arthritis patients is frequently associated with increased mortality. Recently, the incidence of vasculitis seems to be declining.

Turesson C et al[66] in 2006 studied the cardiovascular risk among Rheumatoid Arthritis patients with severe extra articular manifestations and a relation between them. They found that this relation is not because of any differences in age, sex, smoking habits, presence of Rheumatoid Factor or erosive changes in the joints and arrived at a conclusion that extra articular manifestations remain a main feature in determining the risk of cardiovascular disease in patients with rheumatoid arthritis.

Among the extra articular manifestations, most commonly occurring is rheumatoid nodules present in about 20% of patients with RA. They are usually seen at sites which are subjected to constant pressure like extensor surfaces of forearm and posterior surface of the tendoachilles. Definite diagnosis of rheumatoid nodules is by biopsy, which on histopathological examination will demonstrate 3 zones – (1)outer zone with granulation tissue, (2)middle zone having pallisading macrophages, and (3)central zone with necrotic material.[67]

The disease process also affects several other systems.

Numerous morphological changes have been demonstrated in the kidneys in patients with RA[161920] and involvement of the kidneys is thought to be a common reason for death in Rheumatoid Arthritis.[6869]

Boers M et al[16] in their autopsy based study, noticed that patients with Rheumatoid Arthritis showed certain morphological changes in the kidneys like sclerosis of the kidney(90%), rheumatoid vasculitis (14%) with renal

involvement in 8%,amyloidosis (11%), membranous nephropathy(8%), and focal glomerulonephritis(8%). They recommended that these changes could be due to both rheumatoid and non-rheumatoid disease as suggested by clinical data.

Ramirez G et al[19]conducted an autopsy based study on 76 patients having rheumatoid arthritis, performed at the University of Utah and Salt Lake Veterans Administration Medical Center.

The most common among the renal changes were interstitial fibrosis(46%) and arteriolar wall thickening without significant evidence of hypertension(54%).Only 7% had renal amyloidosis. Although not clinically relevant, 9% of rheumatoid arthritis patients were detected to have creatinine levels above 2mg/dl. Furthermore, it was seen that azotemia was not a common cause of mortality in these patients.

Sellars L et al[20]did a study where they took renal biopsies from 30 patients having Rheumatoid Arthritis and analysed clinical evidence of renal disease; biopsy was taken only from those who showed normal intravenous pyelogram, thereby excluding patients with papillary necrosis and chronic pyelonephritis. The biopsy materials were examined under light, electron and immunofluorescence microscopy. Out of the 30 patients,there were 13 cases showing mesangial change, 9 cases of membranous glomerulopathy, 4 cases of tubulointerstitial nephritis, 2 cases of focal glomerular sclerosis, 1 case of amyloidosis and 1case of diffuse glomerulonephritis frequently with

epithelial crescent formations. All those having membraneous glomerulopathy and 6 among the 13 patients showing mesangial changes, had been given either gold or penicillamine. There wasn't any evidence suggestive of "glomerulitis" or systemic vasculitis associated with RA.

Laakso et al[21]carried out a study on 1000 Rheumatoid Arthritis patients(500 males and 500 females) aged ≥ 40 years along with an age and sex matched control group, and followed them up for 10 years. A higher mortality rate was observed among Rheumatoid Arthritis patients (irrespective of their gender), when comparing with the control population. This was mainly due to increased death from infections and diseases affecting the heart and kidneys. In the 10 year follow up period , 31 patients having Rheumatoid Arthritis (12 male and 19 female) and one male patient among the control group died from amyloidosis,and 42 Rheumatoid Arthritis patients (19 male and 23 female) and one male patient among the control group died due to renal disorders.

The major reasons for mortality due to renal diseases were infections and chronic glomerulo nephritis.

Boers et al[22] and **Bird** et al[23]suggested that subclinical involvement of the kidneys is usual in Rheumatoid Arthritis and for detection of protein excreted in urine, albustix and other simple tests may not have the necessary sensitivity. In order to identify the presence of microalbuminuria at an earlier stage, there need to more sensitive tests available for use.

Molitch et al[24] from the American Diabetes Association(ADA) in 2004 formed a definition for Microalbuminuria as urinary albumin excretion of 30–299 mg/ 24 h or albumin/creatinine ratio of 30-299 μg albumin/mg creatinine.

Wiseman MJ and **Viberti G**[70] in 1985 interpreted the mechanism by which microalbuminuria is present in diabetic nephropathy. They suggested that permeability of the glomerulus to albumin depends on the presence of negative endothelial charge and also size selectivity. They found that the negative charge present on the glomerular basement membrane is due to a constant glycoprotein and this is responsible for the controlled passage of anionic proteins across the membrane. They also found that presence of microproteinuria signifies a defect at the glomerular level, and albumin and IgG form the major constituents. Microproteinuria is seen to be related with poor control of blood sugar levels and also mild increase of arterial pressure. This may be due to the hemodynamic changes occurring in the glomerulus and loss of endothelial charge selectivity, and it was seen that microproteinuria can be reversed by correcting hyperglycemia and controlling blood pressure levels. A continuous fall in GFR would occur once a positive dipstic test (i.e. total urinary protein excretion more than0.5 g/day) is observed and patient becomes hypertensive. When the GFR becomes as low as 20 ml/min/1.73 m^2, comparatively more IgG than albumin will be filtered resulting in a low selectivity proteinuria. This is consistent with changes in

the size selectivity features of the glomerular filter. They observed that controlling blood sugar levels have no effect on GFR but controlling blood pressure and following a low protein diet can slow down GFR, most likely by modifying the continuous hemodynamic disturbances occurring in the remaining glomeruli. They also found that in view of the fact that microalbuminuria is reversible at an early stage, it gives the possibility of achieving prevention of the later irreversible stage of end stage renal failure.

Gosling P et al[71] in 1989 observed loss of charge selectivity of the glomerulus in those with microalbuminuria irrespective of whether they are diabetic or not.

Other likely mechanisms of microalbuminuria include the following:

Stender S and **Hjelms E**.[72] in 1987 proposed the systemic transvascular albumin leakage: transcapillary escape rate of albumin (TERalb) is defined as the fraction of the intravascular mass of albumin (IVMA) going through the vascular bed per unit time. The TERalb is an overall measure of the permeability of the vascular bed in vivo to various macromolecules .Presence of microalbuminuria suggests systemic transvascular leakiness for albumin, and also allowing increased lipid insudation into the wall of large vessels; hence microalbuminuria may be related to atherogenesis.

Lindberg G et al[73] in 1992 described that sialic acid has an effect on many haematological factors, transvascular permeability and lipid accumulation in the arterial wall. Studies revealed that in those without

diabetes, an increased serum sialic acid levels in association with increased albuminuria is predictive of atherosclerotic vascular disorder.

Clausen P et al[74] in 2001 in their study observed that mild increase in excretion of urine albumin is found to be related with defective conduit arterial dilatory capacity in clinically healthy study population. This defect could be the result of decreased dilatory response to endogenous or exogenous nitric oxide and it may add to the cardiovascular risk in those with elevated urine albumin.

Lee P et al[75]conducted a study in 1993 which revealed increased levels of certain prothrombotic(fibrinogen and factor VII C) and anti thrombotic factors(protein C, protein S and antithrombinIII) in type 1 diabetes subjects with microalbuminuria, and also in those having hypertension. These factors were thought out to be a good indicator of endothelial dysfunction.

Kuusisto J et al[76] in 1995 observed the role of insulin in smooth muscle cell proliferation, stimulation of LDL binding muscle cells, fibroblasts and monocytes, and in vitro cholesterol synthesis in monocytes and found out that patients with elevated insulin levels and microalbuminuria have high risk of cardiovascular disease.

Svenson KL et al [77] in 1988 found a comparatively better insulin response and impaired glucose handling in patients with active Rheumatoid Arthritis than the healthy control population. **HällgrenR** and **Berne C**[78] in 1983 and **Dessein PH** et al[79] in 2002 saw that administration of certain drugs

having anti-inflamatory action like corticosteroids and DMARDs resulted in a temporary decline in insulin resistance.[777879]

The increased risk for developing cardiovascular and cerebrovascular disease in patients having micoalbuminuria may be attributed to a certain extent to homocysteinemia, which is an atherogenic risk factor. [24]

Bakris GL[80] in his journal on clinical hypertension published in 2001 suggested that the earliest clinical evidence of diabetic nephropathy is microalbuminuria. He also observed various studies suggesting microalbuminuria as a major cardiovascular risk factor. Presence of microalbuminuria in patients with type 2 diabetes or essential hypertension increases the risk of early death from cardiovascular diseases. Microalbuminuria also denotes atherosclerosis and abnormal permeability of the vessels. Microalbuminuria in non-diabetic patients with essential hypertension is shown to have an association with high blood pressure levels, hypercholesterolemia, and decreased serum HDL (high-density lipoprotein)cholesterol. Gathering all these information,a concept was developed. It suggested that "occurrence of microalbuminuria is the kidney's warning to the physician/patient of the increased risk for developing cardiovascular diseases and that there is a defect with the vasculature". By controlling blood pressure levels, reduction of microalbuminuria can be achieved, and also prevent the development of overt proteinuria.

In the two studies conducted in the early 1980s by **Parving HH** et al [81] in Denmark and **Viberti GC** etal[82] in London, they mentioned the significance of MA. They independently suggested that an increased level of microalbuminuria is a strong predictor of progression to diabetic kidney disease. They observed that these levels of AER (Albumin Excretion Rate) can be reversed, and intervention at the appropriate time may prevent diabetic nephropathy. Microalbuminuria predicts the progression to overt diabetic renal disease and kidney failure.

Mogensen CE[83] in 1984 noticed clinically detectable increased urinary protein excretion and greater mortality in type 2 diabetes patients with micoalbuminuria. There are a number of studies suggesting microalbuminuria as a predictor of development of nephropathy and also higher cardiovascular risk and overall mortality, in patients with diabetes mellitus.

Allawi J et al[84] in 1990 observed the relation between persistent microalbuminuria and presence of dyslipidemia, hypertension and obesity, in type 2 diabetes.

The ADA in 1998, considered to include presence of MicroAlbuminuria as a risk factor for ischemic heart disease in patients with DM.[85]

Jensen JS et al [86]in 1995 suggested that positive microalbuminuria is a risk factor for atherosclerosis.

A high morbidity and mortality due to atherosclerotic cardiovascular disease were seen in those having a mildly increased UAER(urinary albumin excretion rate), known as microalbuminuria. Hence, the relationship between microalbuminuria and the well-known risk factors for atherosclerosis was reviewed in clinically healthy population. Among the healthy 40-65 year-old participants with microalbuminuria, who were examined within the first 21 months of The Copenhagen City Heart Study, 28 were chosen for the study. The control group selected for the study included an age- and sex-matched group of 60randomly chosen subjects with normal urinary albumin excretion. Microalbuminuria is thought to be an important predictor of progression to overt diabetic renal disease [82] and hence it was well accepted as a risk factor for the development of cardiovascular disease (CVD).

Microalbuminuria usually shows an association with increased levels of many inflammatory factors whether or not hypertension or diabetes is present .**Barzilay JI** et al[87] in2004 suggested that inflammation preceded the onset of microalbuminuria. They observed that levels of inflammatory markers, age and higher levels of systolic blood pressure show a relationship with microalbuminuria in elderly population, either with or without hypertension or diabetes. Since these are risk factors for coronary artery disease (CAD), these investigations find the relationship between microalbuminuria and CHD.

Diercks GF et al [88]performed a study on 7579 non-diabetic subjects aged between 28 to 75 years chosen from a population based cohort and observed that there is an independent association between microalbuminuria and ischemic ECG abnormalities. This suggested that microalbuminuria has an added significance when compared to the usual risk indicators in predicting cardiovascular disease in non-diabetics. They proposed that evaluating for the presence of microalbuminuria would aid in early recognition of those at high risk for coronary heart disease.

Festa A et al[89]proposed that microalbuminuria represents a widespread damage of the vessels and that it has a strong association with inflammation which is seen underlying every stage of atherosclerosis.

Neil A et al[90] in 1993 performed a study on 249patients with NIDDM (Non Insulin Dependent Diabetes Mellitus). The results obtained from this population-based cohort confirmed that microalbuminuria is a good predictor of mortality risk in patients with NIDDM. Comparing with the prospective studies on conventional risk factors for cardiovascular disease in patients with NIDDM, there was evidence suggesting microalbuminuria as an independent predictor of increased mortality.

A Study by **Agarwal** et al[91] in 1996 showed increased prevalence of microalbuminuria in patients with hypertension, especially among those in whom blood pressure characteristics are related with increased cardiovascular risk, such as salt sensitivity and an atypical diurnal variation in blood

pressure. They came to a conclusion that presence of microalbuminuria allows early identification of development of renal and cardiovascular complications in hypertensive patients.

There are several studies showing the association between microalbuminuria and other atherogenic risk factors like hypertension, hyperlipidemia, and smoking in the general population. **Damsgaard EM** et al[92] in their study conducted in 1990, found out that microalbuminuria is an important predictor of high mortality among elderly individuals.

Microalbuminuria is seen to be present in the earlier stages of acute myocardial infarction and is thought of as an independent predictor of early death in this disease condition. It was also seen that microalbuminuria is proportional to infarct size.

Gosling et al[93] in 1991recommended that early increase in urinary albumin concentration is valuable in differentiating a myocardial infarct from an angina. A higher level of excretion of urinary protein seems to be an early and proportionate response to myocardial infarction.

Roine I94 in 1993 established that microalbuminuria is 94% specific in differentiating bacterial from aseptic meningitis. He observed that microalbuminuria is a potential acute phase reactant for the early assessment of severity of bacterial meningitis, and that its estimation is easy and involves non invasive procedure.

Shearman et al[95]observed peaking of micoalbuminuria in cases with acute pancreatitis 36 hours following admission. They also observed development of serious complications in association with higher levels of microalbuminuria.

Pallister et al [96]observed in their study that in trauma patients 8 hours after admission, levels of microalbuminuria is a good predictor for development of ARDS (positive predictive value - 85% ; negative predictive value - 95%).

Mykkanen L et al[97]observed that microalbuminuria is associated with thickness of carotid artery intima-media, suggesting that it may be an indicator of early atherosclerotic changes in the carotid artery, and points towards a possible relationship between microalbuminuria and mechanism of atherothrombotic stroke.

Mahmud N et al[98] in 1994 came to the conclusion that microalbuminuria is most likely the result of an acute phase reaction and it serves as an easy, quick to perform, and economical test, capable of monitoring disease activity as well as treatment response in inflammatory bowel disease.

Hickey NC et al[99] in 1990 observed in their study that microalbuminuria, which was formerly demonstrated to represent vascular permeability, was seen to increase considerably following exercise in claudicants.

Tagle et al[107] in 2003 suggested microalbuminuria as a strong predictor of cardiovascular morbidity and mortality, clinical nephropathy, and development of kidney disease in high-risk individuals. Screening is advised for patients with type 2 diabetes, elderly patients having type 1 diabetes, and elderly patients with stage 2 hypertension or higher(i.e.,≥ 160/100 mm Hg). There are numerous pathways linking microalbuminuria and vascular disease. Several factors like resistance to insulin, central obesity, reduced levels of HDL cholesterol, increased triglyceride levels, systolic hypertension, absence of fall in blood pressure levels during night time, salt sensitivity, endothelial dysfunction, hypercoagulability, defective fibrinolysis and dysfunctioning of the kidneys are seen to be associated with microalbuminuria. This gives sufficient evidence supporting the role of microalbuminuria in predicting vascular disease among high risk individuals. Therefore, a regular screening for detecting the presence of microalbuminuria would be helpful in recognising those patients at increased risk of developing cardiovascular disease and they require early intervention, intensive treatment, and close follow up.

Nakamura M et al[103] in 2004 observed a significant association between low-grade inflammation as reflected by high sensitivity CRP levels and microalbuminuria, suggesting that microalbuminuria may be a useful indicator of systemic low-grade inflammation and a well recognised risk factor for cardiovascular disease among seemingly healthy population.

Pedersen LM et al[100] (1995) conducted a study on 65 rheumatoid arthritis patients attending 2 rheumatology clinics and they were compared with 51 age and sex matched controls. Their study showed that 27.7% of rheumatoid arthritis patients and 7.8% of the controls were detected to have microalbuminuria (with urine albumin to creatinine ratio ranging between 3-30 mg/mmol in either or both urine specimens collected).There was significant association between urine albumin creatinine ratio and CRP, and disease duration. It was also observed that therapy involving the use of gold and pencillamine had increased risk of developing microalbuminuria. No significant association was found between ESR (erythrocyte sedimentation rate) and MA.

In a study by **Bhatt** et al[101], 30% of rheumatoid arthritis patients were detected to have microalbuminuria, especially those in whom the disease was severe and was present for a long duration.

Saito M et al[102] in 1993 studied the relevance of microalbuminuria in rheumatoid arthritis. The study was performed on 138 rheumatoid arthritis patients not having microalbuminuria. Estimation of microalbuminuria was done by double antibody radioimmunoassay (RIA)method in the ambulatory urine sample. At the same time, urinary (U) beta 2-microglobulin (BMG) and N-acetyl-beta-D-glucosaminidase (NAG) were also estimated. U-Alb indices (MA/U-creatinine ratio) in rheumatoid arthritis, osteoarthropathy (OA), and normal controls were 25.7 ± 38.2,11.4 ± 11.5 and 7.7 ± 3.5 respectively. It

was seen to be significantly higher in rheumatoid arthritis patients when compared with the values in patients having osteoarthropathy and in normal controls. They observed higher values of U-Alb index in rheumatoid arthritis patients receiving lovenzarit disodium and gold sodium thiomalate (GST).It was found that U-Alb indices were not associated with the clinical findings, U-BMG indices and U-NAG indices in patients with Rheumatoid Arthritis. U-Alb index, U-BMG index and U-NAG index were sequentially calculated in a rheumatoid arthritis patient who had massive MA while on treatment with GST, and it was observed that first U-Alb index increased, then U-NAG index and ultimately there was also an increase in U-BMG index. This shows that U-Alb indices are increased in rheumatoid arthritis patients without macroalbuminuria, and serial estimation of microalbuminuria in patients having rheumatoid arthritis, particularly those on DMARDs will be helpful in detecting subclinical glomerular insult.

Nordin et al[104] in 1996 performed a study on 65 patients having RA comparing them with 51 controls matched by age and sex. There was significant elevation of microalbuminuria in rheumatoid arthritis patients (27.7%) when compared with the control population (7.8%).The median disease duration was significantly higher in patients having microalbuminuria (11.2 v 7.8 years; $p < 0.001$). CRP was identified as an important indicator of disease activity. They also found a significant correlation to therapy with gold and pencillamine. In conclusion, microalbuminuria measured by

immunochemical methods is a simple sensitive test for identifying subclinical damage to the kidney and could be a sensitive marker of disease activity in rheumatoid arthritis. Microalbuminuria can be utilised for monitoring early subclinical dysfunction of the kidneys and damage caused to the kidneys by drugs, in patients having rheumatoid arthritis.

Monica V et al[105] in 2013 observed that the increased prevalence of microalbuminuria is associated with Rheumatoid Arthritis disease activity based on ESR and CRP. They also found a correlation between MA and increase in disease duration and number of joints affected. Thus, they arrived at a conclusion that microalbuminuria appears to represent the disease activity in rheumatoid arthritis.

In 1963, **Keen** and **Chlouveraskis**[106]detailed the first specific radioimmunoassay (RIA) for urine albumin. Radioimmunoassay for microalbuminuria is the "gold standard" for the measuring urine albumin. This method involves a double antibody technique in which albumin present in the test sample binds to specific antibody sites competing with a fixed amount of ^{125}I labelled albumin. Separation of bound and free forms of albumin is achieved by adding a second antibody immunoabsorbent and thereafter by centrifugation and decanting. C counter is used for measuring the radioactivity in the pellet.

Concentration of albumin in the sample is inversely proportional to radioactivity. Radioimmunoassay shows a sensitivity of 0.3mg/l. Rheumatoid arthritis is a chronic inflammatory disease with varied disease expression. A range of variables(core-set variables) are being chosen for assessing the status and course of disease activity in rheumatoid arthritis, as well as disability and damage to the joint.[108109]

Van Riel PL[108] in 1992 recommended a set of core variables that can be helpful in assessing the status and course of Rheumatoid Arthritis disease activity, disability and joint damage.

Felson DT et al[109] in 1993 formed a committee on outcome measures in Rheumatoid Arthritis clinical trials . A core set of disease activity measures was suggested by them which included tender joint count, swollen joint count, patient's assessment of pain, patients and physician's global assessment of disease activity, patient's assessment of physical function, and laboratory estimation of one acute-phase reactant. All these measures collectively illustrate the wide variety of improvement in Rheumatoid Arthritis, and all of them show at least a moderate sensitivity to change. Most of them are a good predictor of physical disability, radiographic changes, death and various other significant long term outcomes in Rheumatoid Arthritis. Other disease activity measures often used in clinical trials were not preferred for anyone of a number of reasons, including insensitivity to

alteration or repetition of information provided by one of the core variables (e.g., tender joint score and tender joint count).

The committee also suggests specific ways of evaluating each outcome.

Comparing with the various available disease activity variables separately, DAS offers a more suitable measure of disease activity in Rheumatoid Arthritis.[3536]

Van der Heijde DM et al[36]in 1993, performed a prospective study on 113 patients having early rheumatoid arthritis for a period of 3 years. Based on the clinical decision of six rheumatologists, they developed a disease activity score (DAS). In accordance with explicit rules, the study subjects were divided into two groups – those with high disease activity and those with low disease activity. A disease activity score (DAS) can be defined by means of a variety of statistical methods, including discriminant analysis and multiple regression analysis, and comprises of the variables, Ritchie articular index, number of swollen joints, ESR (erythrocyte sedimentation rate), and general health measured on a visual analogue scale.

Prevoo et al[110] in 1995 developed the modified DAS by recognized discriminate analyses and approved for criterion, co relational, and construct validity.

Investigation as to how the duration of the disease influence the disease activity scores (DAS) composition was also carried out, and they did not observe any influence by disease duration. The Modified disease activity

score (DAS) which included 28-joint counts, is capable of differentiating between those with high and low disease activity (as determined by clinical opinion of rheumatologists). Since the modified DAS contains more inclusive joint counts, it is being considered as a valid disease activity score. The DAS28 (similar to the original DAS), comprises of a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), erythrocyte sedimentation rate (ESR), and an optional general health assessment on a visual analogue scale (range 0-100).**Harikrishnan Aggarval** et al[111]conducted a study based on the histopathology and functional status of the kidneys in 50 patients having rheumatoid arthritis. They observed that those with severe disease activity score (DAS) score usually showed involvement of the kidney. The study subjects were grouped into two based on the disease duration, with each group having 25 patients. Those patients with disease duration less than 5 years were grouped under group 1, and more than 5 years under group 2. It was found that the mean DAS was greater in group 2.

V Raveendran et al[112] from SMS medical college and hospital, Jaipur, India, Performed a study about subclinical renal dysfunction in patients with rheumatoid arthritis, and observed significantly higher urine albumin excretion in patients having active disease (DAS28> 3.2) than those who were in remission (DAS28 < 2.6). 40 each of rheumatoid arthritis patients and healthy controls were taken for the study.

Microalbuminuria was significantly greater in rheumatoid arthritis patients (30%) than controls (5%).Also, rheumatoid arthritis patients with microalbuminuria were seen to have a significantly longer duration of the disease than those with normoalbuminuria. There was significant association between urine albumin excretion and erythrocyte sedimentation rate (ESR).

MATERIALS AND METHODS

The study was conducted on 60 patients attending the rheumatology out patient department of Thanjavur Medical College, Thanjavur. Total study duration was 6 months from the date of ethical clearance. It was a cross sectional study.

Inclusion criteria

After clinical assessment and laboratory investigations, those patients aged above 12 years fulfilling the Modified ACR (American College of Rheumatology Association) criteria (1987) for Rheumatoid Arthritis were included in the study.

Exclusion criteria

Those patients having hypertension, diabetes mellitus, previous history suggestive of renal disease and paediatric age group less than 12 years were excluded from the study.

Sample size, n=60 (n=4pq/l² p-prevalence in previous study, q=100-p, l=20% of p)

An informed consent was obtained from all patients.

A detailed history was taken from all the patients and, age, sex, duration of RA, presence and duration of morning stiffness, chest symptoms, list of painful joints ,presence of other systemic disease and presence of extra-articular manifestations of RA were recorded.

Examination

All joints were systematically examined for the presence of any tenderness, swelling, or deformity as well as the possible range of movements at these joints. Examination of the cardiovascular, respiratory, gastrointestinal, and nervous system was done. Patients were carefully observed for the presence of any extra articular manifestations and the findings were documented.

Calculation of Disease activity score (DAS28) was done for all of them by means of DAS28calculator for ESR.

Investigations

emphasis was given for the following investigations.

Erythrocyte sedimentation rate

ESR was measured using Westergren method. Venous blood was anti-coagulated by trisodium citrate dehydrate in the ratio of 4:1 and well mixed by gentle, repeated inversion and used to fill a Westergren-Katz tube up to the

0(zero) mark. Subsequently, the tube was placed vertically in a rack, which is protected from direct sunlight, draught or vibration and incubated at room temperature for 1 hour (60 minutes).

After one hour, the distance (in mm) from the bottom of the surface meniscus to the top of sedimenting red cells was noted and reported as the ESR value. This test was done within 2 hours of collecting blood samples.

Rheumatoid factor (IgG)

A quantitative assay was done employing a latex fixation lab kit. A value above 36 IU/ml was considered to be positive.

C - reactive protein

A quantitative assay was done employing ELISA technique. Values >6mg/l were taken as positive.

Microalbuminuria(MA)

Assessment of Urine albumin-creatinine ratio (U.ACR) from spot urine sample was done by radioimmunoassay. It gives a quantitative estimation of microalbuminuria.

Routine investigations

Haemoglobin, total leukocyte count, differential counts, blood urea ,serum creatinine and blood sugar estimation were done.

Disease Activity Scale score (DAS28)

DAS28 = 0.56 x √(28TJC) + 0.28 x √(28SJC) +0.70 x Ln(ESR) + 0.014 x VAS

- TJC-Total tender joints
- SJC-Total swollen joints
- ESR-Erythrocyte Sedimentation Rate in mm/hr
- VAS-Visual Analogue Scale (patient puts a vertical mark on a 100 mm Scale corresponding to their general health or global disease activity. Measurement is taken from the left hand side using a ruler.)

Interpretation:

The DAS28 score provides a number on a scale from 0 to 10 representing the present RA disease activity.

- Remission: DAS28 $\leq$ 2.6
- Low Disease activity: 2.6 < DAS28 $\leq$ 3.2
- Moderate Disease Activity: 3.2 < DAS28 $\leq$ 5.1
- High Disease Activity: DAS28 >5.1 [38]

Statistical methods

The significant association of clinical factors between patients with and without the presence of MA has been found out using Chi square test/Fischer Exact test. Odds ratio has been used to find the significant strength of relationship of factors in association with microalbuminuria. Student t test (two tailed, independent) has been used to find the significance of investigation parameters between the two patient groups.

Statistical software

SPSS 20.0 was used for data analysis and Microsoft word and excel have been used to generate graphs, tables etc.

Ethical consideration

Compilation of data required for the study was commenced only after getting clearance from the ethical committee. The privacy of the patient and the confidentiality of the clinical data were maintained during the study. A written consent was obtained from every patient before including him/her in the study. Those who did not consent were excluded from this study. No additional expenses were needed by the patients as part of this study.

OBSERVATIONS AND RESULTS

This study is a cross sectional study with case control comparison, done in Thanjavur Medical College, Thanjavur, between January 2016 and August 2016. 60 patients of RA diagnosed by means of modified ACR criteria (1987) were included in the study once they had satisfied the inclusion criteria. Patients with hypertension, diabetes mellitus or renal diseases, and individuals aged below 12 years were excluded from this study.

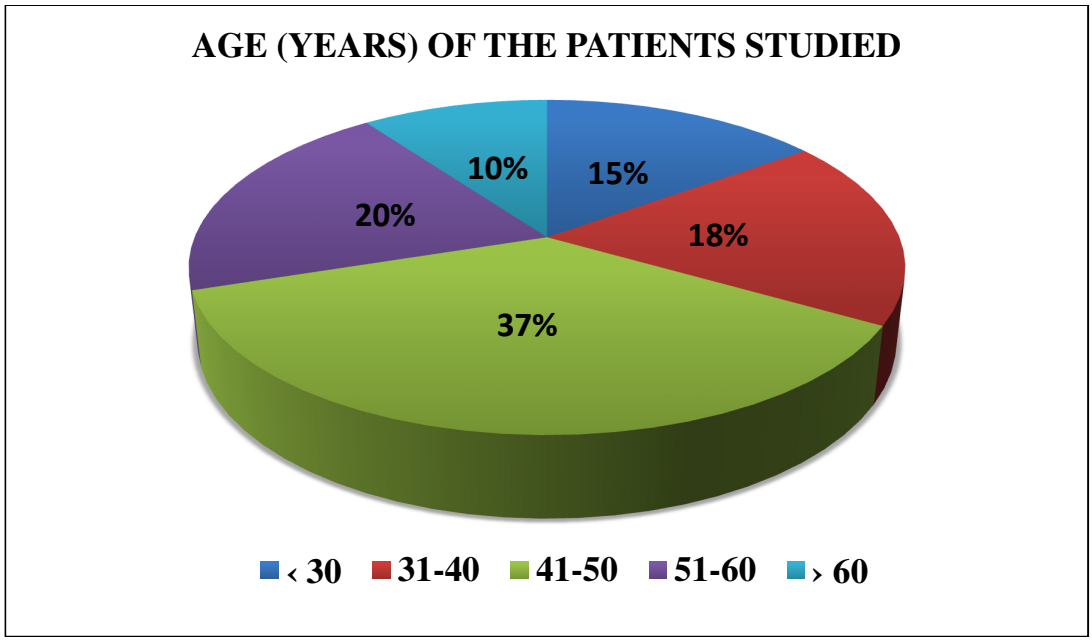
Age and sex distribution

The age group of the study population chosen ranged between 14 and 81 years with a mean of 44.55 yrs (SD 13.767).Among the study population, the age of males ranging from 24 to 81 years showed a mean value of 46.529 yrs (SD-13.005), and the age of females ranging from 14 to 72 years showed a mean of 43.767 yrs (SD-14.128). 55% of the study population belonged to the age group of 31 to 50 years; most of them (36.7%) belonged to the age group of 41 to 50 years.

Table 1.Age (years) of patients studied

AGE (YEARS)	NO: OF PATIENTS (%)
‹ 30	9(15)
31-40	11(18.3)
41-50	22(36.7)
51-60	12(20)
› 60	6(10.0)
Total	60(100)

Figure 1.Age (years) of patients studied

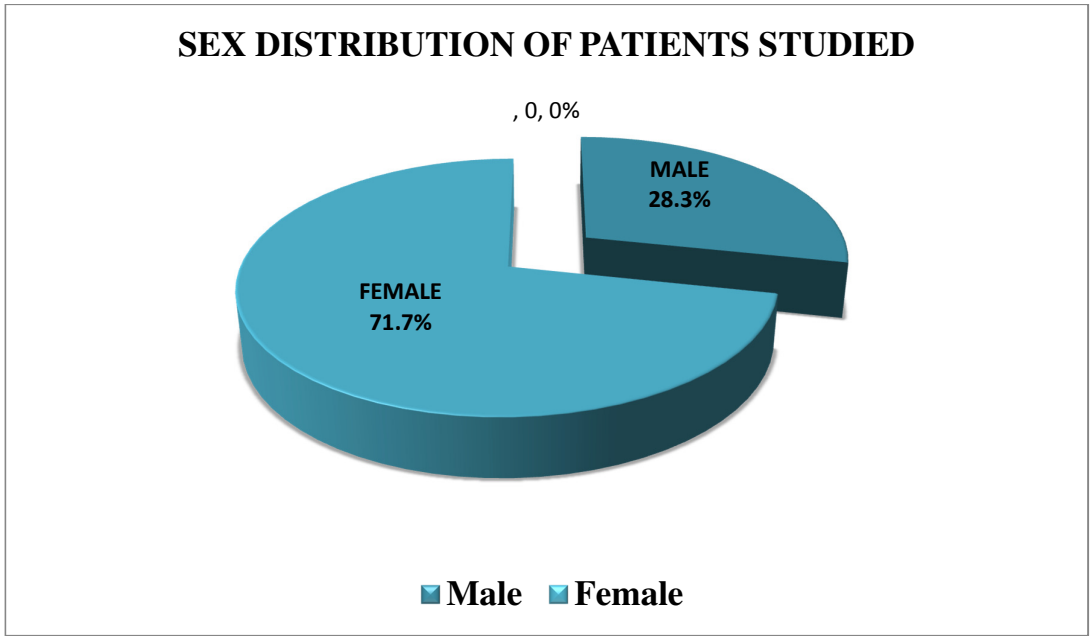


Out of the total 60 members in the study group, 43 were females (71.7%) and 17 were males (28.3%).

Table 2.Sex distribution of patients studied

SEX	NO: OF PATIENTS (%)
Male	17(28.3)
Female	43(71.7)
Total	60(100)

Figure 2: Sex distribution of patients studied



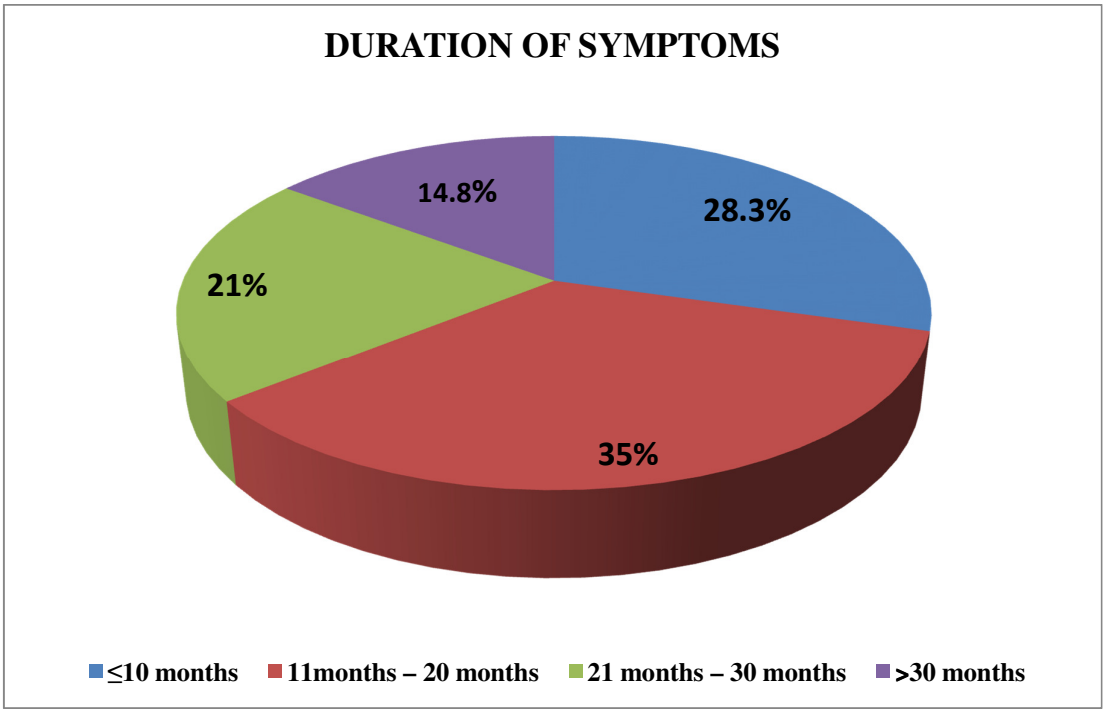
Duration of symptoms

The mean duration of symptoms among Rheumatoid Arthritis patients was 17.88 months, ranging from 3 to 60 months, 35% of patients had symptom duration ranging from 11 to 20months.

Table 3: Duration of symptoms

Duration of symptoms (months)	No. of patients(%)
≤10 months	17(28.3)
11months – 20 months	21(35.0)
21 months – 30 months	13(21.7)
30 months	9(15.0)
Total	60(100)

Figure 3: Duration of symptoms



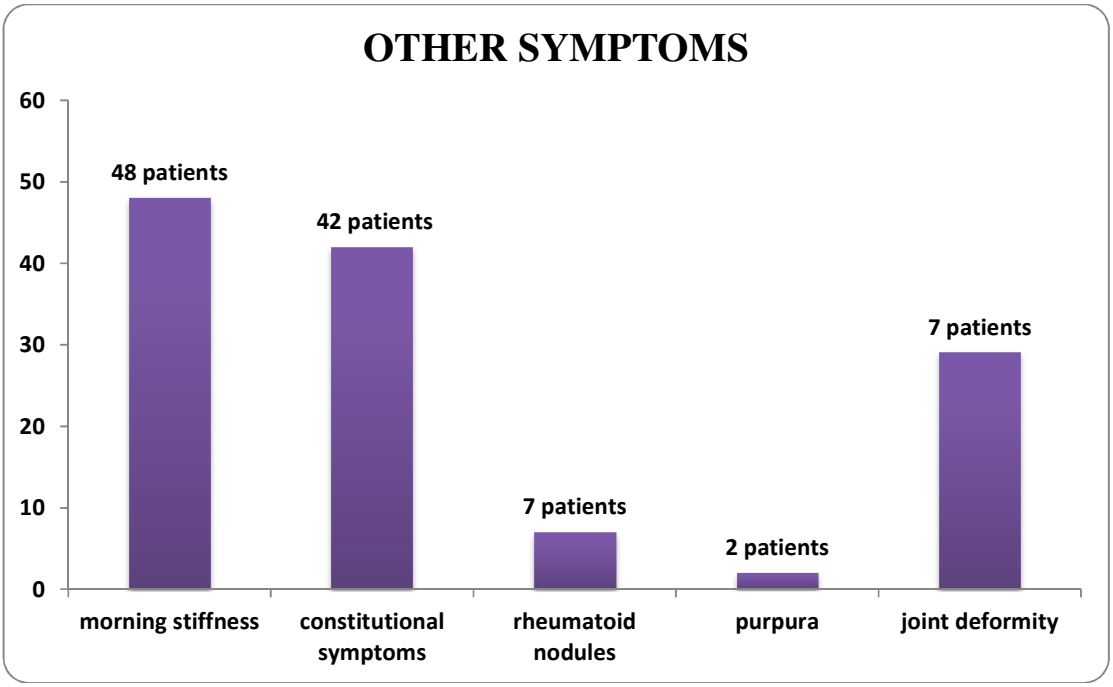
Clinical features and investigations

A positive history of joint pains, morning stiffness and joint swelling was elicited from every patient belonging to the study group. Patients with diabetes mellitus and hypertension, as well as those who gave history of symptoms suggesting cardiac, respiratory or renal diseases like chest pain, palpitation and breathlessness on exertion, pitting pedal edema, paroxysmal nocturnal dyspnoea (PND) or orthopnea were excluded from the study. Those with history of constitutional symptoms such as anorexia, fever and fatigue were included in the study.

80 % of patients had history of morning stiffness lasting for over 60 minutes.

Constitutional symptoms were present in 70% patients.7 patients had rheumatoid nodules. Purpura was present in 2 patients.7 patients showed joint deformities.

Figure 4: Symptoms (other than joint pain and joint swelling)



Joints involved

A total of 4 to 28 joints were affected in patients with rheumatoid arthritis with the mean value for tender joints being 11.2±6.671 and swollen joints being 13.067±6.362. Pain involving 4 – 15 joints was present in 71.7% of patient sand 66.4% showed edema involving 4-15 joints.

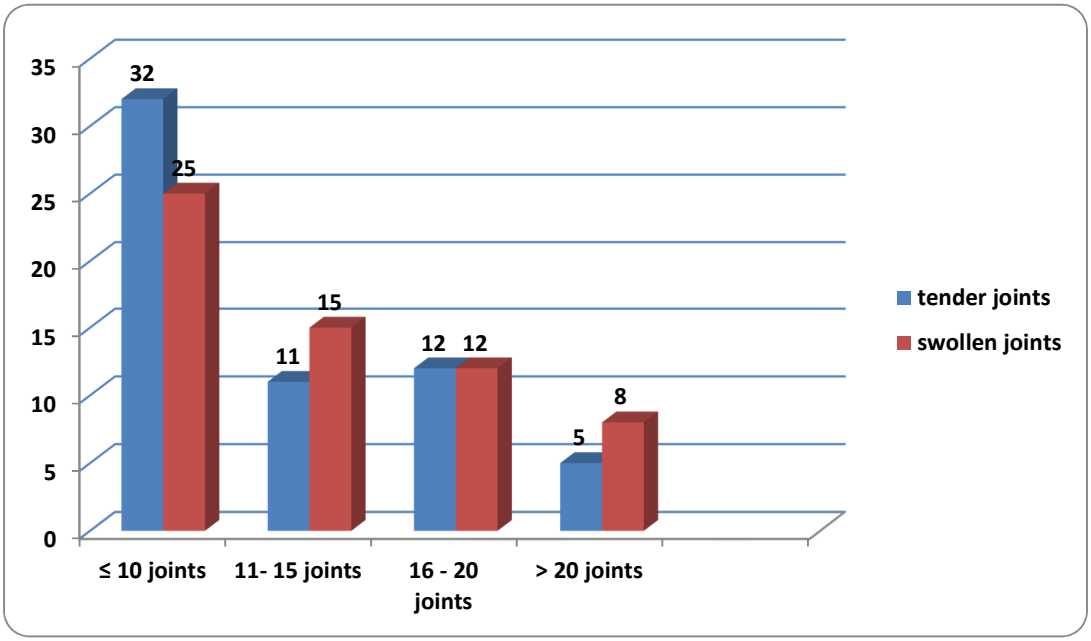
Table 4.Number of tender joints

NUMBER OF JOINTS	NUMBER OF PATIENTS(%)
≤10	32(53.33)
11 – 15	11(18.3)
16 – 20	12(20)
> 20	5(8.3)
Total	60(100)

Table 5.Number of swollen joints

NUMBER OF JOINTS	NUMBER OF PATIENTS (%)
≤10	25(41.7)
11 – 15	15(25)
16 – 20	12(20)
> 20	8(13.3)
Total	60(100)

Figure 5.No. of joints



Pallor was observed in 8 patients, 7 patients showed deformities of the joints, 7 (11.7%) patients were found to have rheumatoid nodules, and 2 patients (3.3%) had purpura. Rheumatoid factor (RF) was positive in 71.7% of patients (43 patients). The values of RF in the study were found to be ranging from 15 to 460 IU/dl.

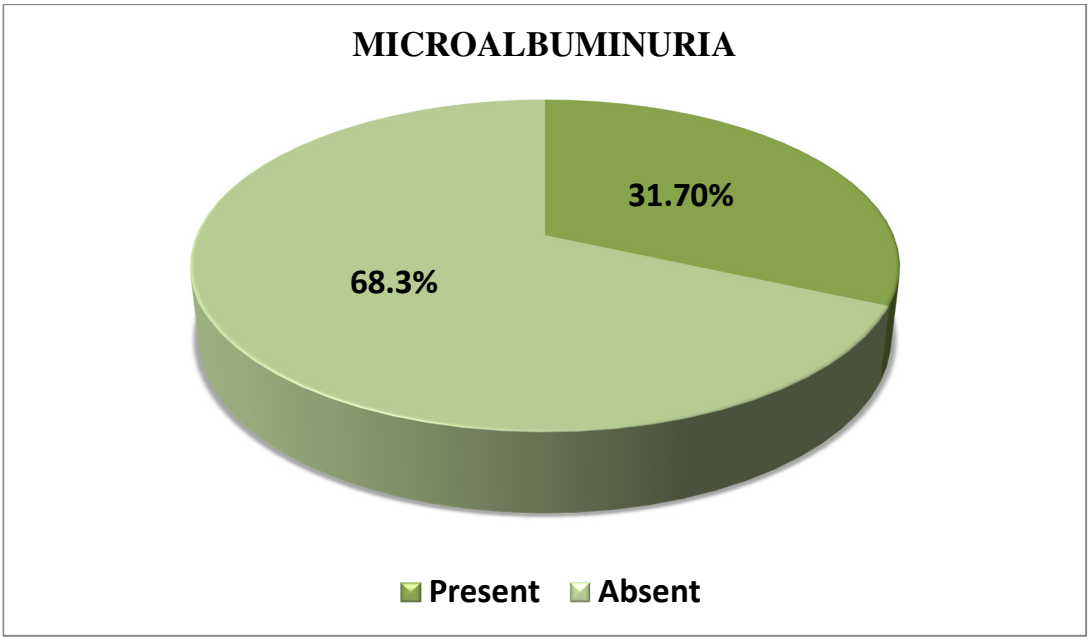
Microalbuminuria

In this study, microalbuminuria(MA) was present in 19 patients (31.7%), which included 3 males and 16 females.

Table 6.Microalbuminuria

MICROALBUMINURIA	NUMBER OF PATIENTS (%)
Present	19(31.7)
Absent	41(68.3)
Total	60(100)

Figure 6.Microalbuminuria



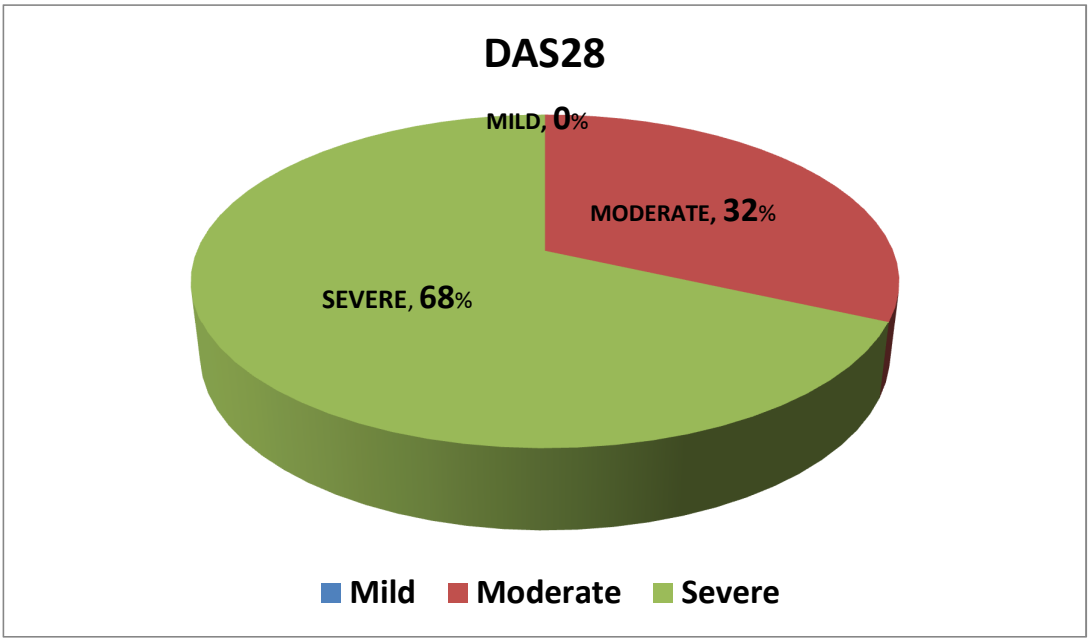
Disease activity (DAS28)

In this study, the disease activity as defined by DAS28 was moderate in 19 patients (31.7%) and severe in 41 (68.3%). None had mild disease activity.

Table 7.DAS28

DAS28	NUMBER OF PATIENTS (%)
Mild	0
Moderate	19 (31.7)
Severe	41 (68.3)
Total	60 (100)

Figure 7.DAS28



Study parameters

Table 8: Mean levels of study parameters(1)

Study parameters	Microalbuminuria		P value
	Absent(n=41)	Present(n=19)	
Age in years, mean ± SD	42.81±13.39	48.32±14.18	0.151 #
Sex – male:female	10:31	7:12	0.492 #
Morning stiffness 60 min, n(%)	32(78.05%)	16(84.21%)	0.835 ##
Constitutional symptoms, n(%)	24(58.54%)	18(94.74%)	0.005**
Patients on treatment, n(%)	11 (26.83%)	10 (52.63%)	0.031**
Deformed joints	7(17.07)	0	>0.05**
Rheumatoid nodules	4(9.76)	3(15.79)	>0.05**
Purpura	2(4.88)	0	>0.05**
Duration of symptoms, mean ± SD	14.73±8.09	24.68±12.06	0.0004*
Number of swollen joints, mean ± SD	11.76±6.31	15.89±5.64	0.018*
Number of tender joints, mean ± SD	9.76±6.25	14.32±6.64	0.0125*
ESR, mean ± SD	50.12± 29.19	80.16±26.67	0.0003*
CRP, mean ± SD	14.63±14.85	27.23±21.26	0.0103*
RAF, mean ± SD	73.63±64.39	187.95±141.27	‹0.0001*
DAS28, mean ± SD	5.2±0.63	6.73±0.65	‹0.0001*

* independent sample t test # ## chi-square test

Of the 19 patients with microalbuminuria in this study, 16(84.2%) had morning stiffness, 18(94.7%) had constitutional symptoms, and 10 patients (52.6%) were on treatment with DMARDs or NSAIDs.

The duration of symptoms was significantly greater in patients with microalbuminuria with mean value of 24.68±12.06 months when compared with 14.732±8.09 in patients with negative MA (p-0.0004).The mean value for swollen joints was 15.89±5.64 in microalbuminuria positive group when compared with 11.76±6.31 in microalbuminuria negative group(P-0.018).The mean value for tender joints was 14.32±6.64 in microalbuminuria positive group when compared with 9.76±6.25 in microalbuminuria negative group. The mean value for ESR was also found to be significantly greater in patients with microalbuminuria (80.16±26.67 v/s 50.12 ± 29.19), with p value 0.0s003.The mean value for CRP was 27.23±21.26 in microalbuminuria positive group when compared with 14.63±14.85 in microalbuminuria negative group (P-0.0103). Only 3 out of 19 MA positive patients (15.79%)had negative RF. The mean value for RF was 187.95±141.27 in microalbuminuria positive group when compared with 73.63±64.39 in microalbuminuria negative group (P‹0.0001). The mean DAS28 score was 6.73±0.65 in microalbuminuria positive group when compared with 5.2±0.63 in microalbuminuria negative group (P‹0.0001)

Table 9: Mean levels of study parameters(2)

Study parameters	DAS28	
	Moderate(n=19)	Severe(n=41)
Age in years, mean ± SD	45.26±12.44	44.22±14.48
Sex – male:female	4:15	13:28
Morning stiffness, n(%)	15(78.95%)	33(80.49%)
Constitutional symptoms, n(%)	13(68.42%)	29(70.73%)
Patients on treatment, n(%)	6(31.58%)	15(36.59%)
Deformed joints, n(%)	5(26.32%)	2(4.88%)
Rheumatoid nodules ,n(%)	3(15.79%)	4(9.76%)
Petechiae, n (%)	2(10.53%)	0
Duration of symptoms, mean ± SD	13.26±7.91	20.02±10.96
Number of swollen joints, mean ± SD	11.79±6.76	13.66±6.16
Number of tender joints, mean ± SD	9.86±7.16	11.9±6.4
ESR, mean ± SD	55.89±25.83	61.37±33.99
CRP, mean ± SD	19.64±16.65	20.01±19.12
RAF, mean ± SD	111.21±85.99	109.19±188.49
MA, mean ± SD	34.47±45.35	94.39±91.48

Out of the 60 patients who participated in this study, 19 were having moderate disease activity and 41 patients with severe disease activity according to the DAS28 score. The mean value for age in patients with moderate disease activity was 45.26±12.44 years while in patients with severe disease activity, it was found to be 44.22±14.48 years. Of the 48 patients with morning stiffness lasting more than an hour, 15 belonged to the moderate disease activity group and 33 had severe disease activity. Of the 42 patients with constitutional symptoms, 13 had moderate disease activity and 29 had severe disease activity. Of the 21 patients receiving treatment for RA, 6 patients belonged to the moderate disease activity group and 15 patients belonged to severe disease activity group. 5 patients with moderate disease activity and 2 patients with severe disease activity showed deformity of joints. 3 patients with moderate disease activity and 4 patients with severe disease activity had rheumatoid nodules. Only 2 patients in the moderate disease activity group and none in the severe disease activity group showed presence of purpura.

The duration of symptoms was higher in patients with severe disease activity with a mean value of 20.02±10.96 months when compared with 13.26±7.91 in patients with moderate disease activity.

The mean value for swollen joints was 13.66±6.16 in severe disease activity group when compared with 11.79±6.76 in moderate disease activity group. The mean value for tender joints was 11.9±6.4 in severe disease activity group when compared with 9.86±7.16 in moderate disease activity group.

The mean value for ESR was found to be 55.89±25.83 in patients with moderate disease activity when compared with 61.37±33.99 in patients with severe disease activity. The mean value for CRP was 19.64±16.65 in moderate disease activity group when compared with 20.01±19.12 in severe disease activity group.

The mean value for RF was found to be 111.21±85.99 in the moderate disease activity group and 109.19±188.49 in the severe disease activity group. The mean value for MA was found to be 34.47±45.35 in the moderate disease activity group and 94.39±91.48 in the severe disease activity group.

Age and microalbuminuria

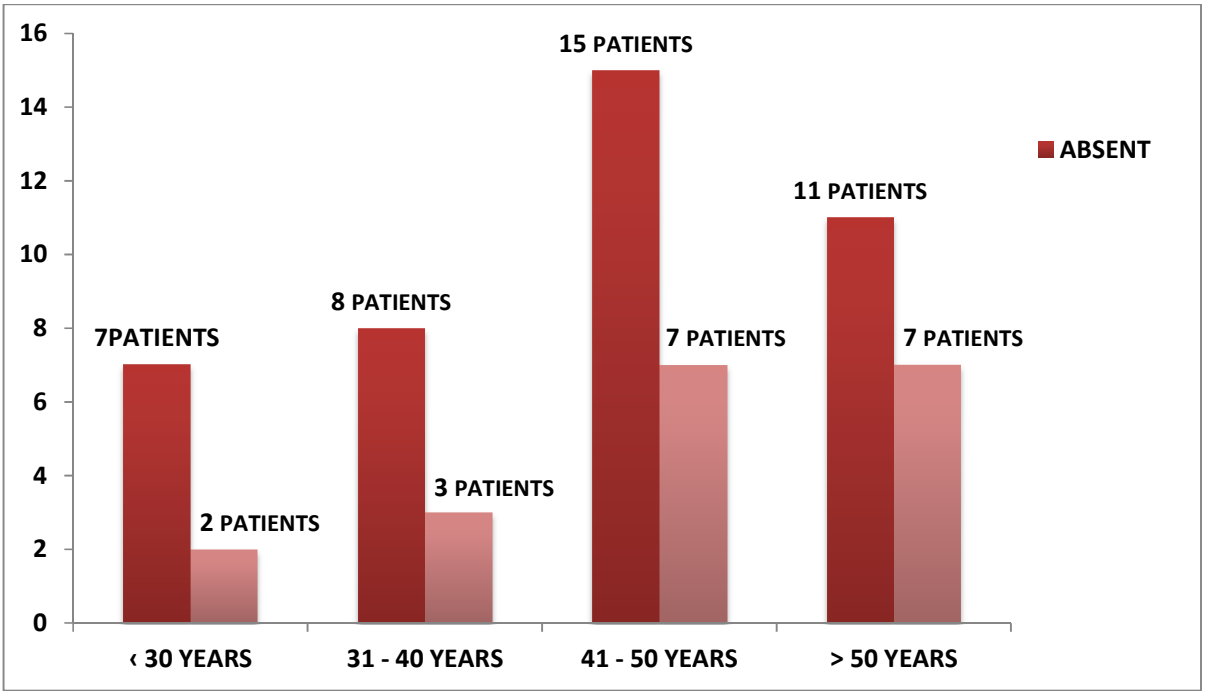
Microalbuminuria was observed to be more frequent in the study population aged above 50 years. P value was not significant (0.628).

Table 10: Association of age in years with presence of microalbuminuria

Age in years	Number of patients	Microalbuminuria		P value
		Absent	Present	
‹ 30	9	7	2	0.628
31 – 40	11	8	3	
41 – 50	22	15	7	
▯ 50	18	11	7	
Total	60	41	19	

Chi-square value for trend is 0.235, degree of freedom 1 and p-value 0.628.

Figure 8: Association between age (years) and Microalbuminuria



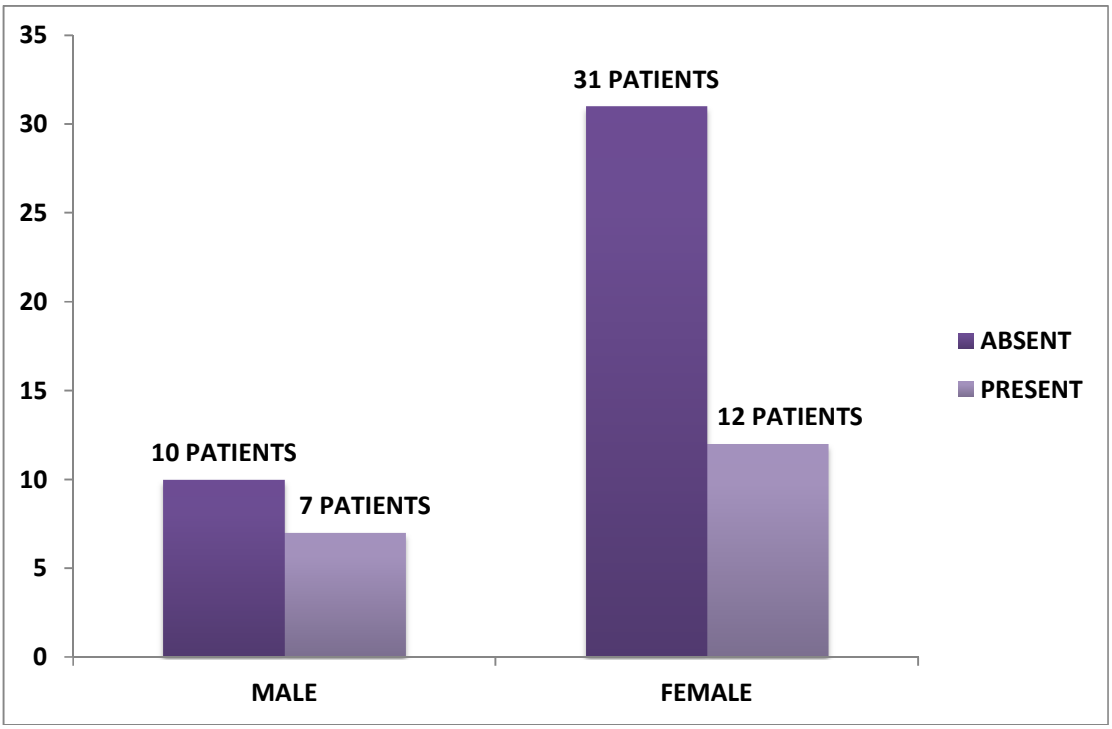
Sex and microalbuminuria

Among the 19 patients in whom microalbuminuria was found to be present, there were 7 males and 12 females. There was no significant association between microalbuminuria and gender of the patient (p value=0.492)

Table 11: Association of sex with presence of microalbuminuria

Sex	Number of patients	microalbuminuria		P value
		Absent	Present	
Male	17	10	7	0.492
Female	43	31	12	
total	60	41	19	

Figure 9: Association between sex and Microalbuminuria



Duration of symptoms and microalbuminuria

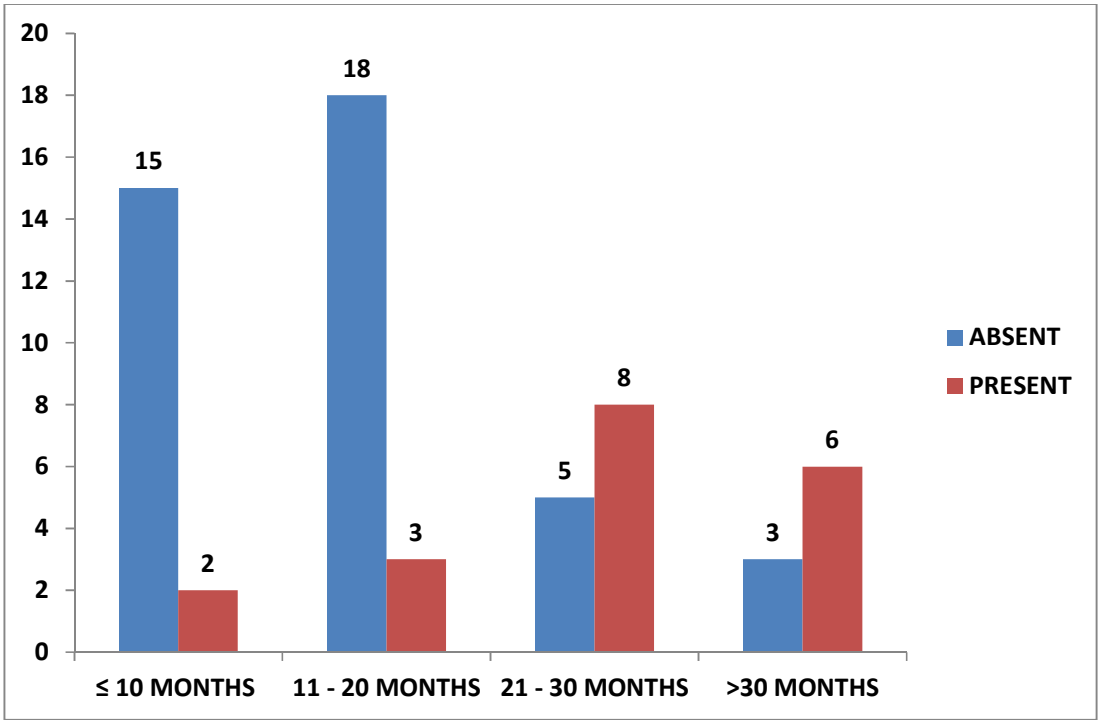
Out of the 19 patients who tested positive for the presence of microalbuminuria, 8 patients (42.1%) had symptoms lasting for 21 – 30 months and 6 patients (31.6%)had symptom duration of more than 30 months (31-60 months). 73.7% of patients were seen to have symptoms lasting for more than 20 months.

Table 12: Association between duration of symptoms and Microalbuminuria

Duration of symptoms (months)	No. of patients	Microalbuminuria		P value
		Absent	Present	
≤10 months	17	15	2	0.0394
11months – 20 months	21	18	3	
21 months – 30 months	13	5	8	
30 months	9	3	6	
Total	60	41	19	

P value was significant (0.0394) in patients with symptoms >30 months. Chi-square value for trend is 4.242, degree of freedom 1 and p-value is 0.0394.

Figure 10: Association between duration of symptoms and Microalbuminuria



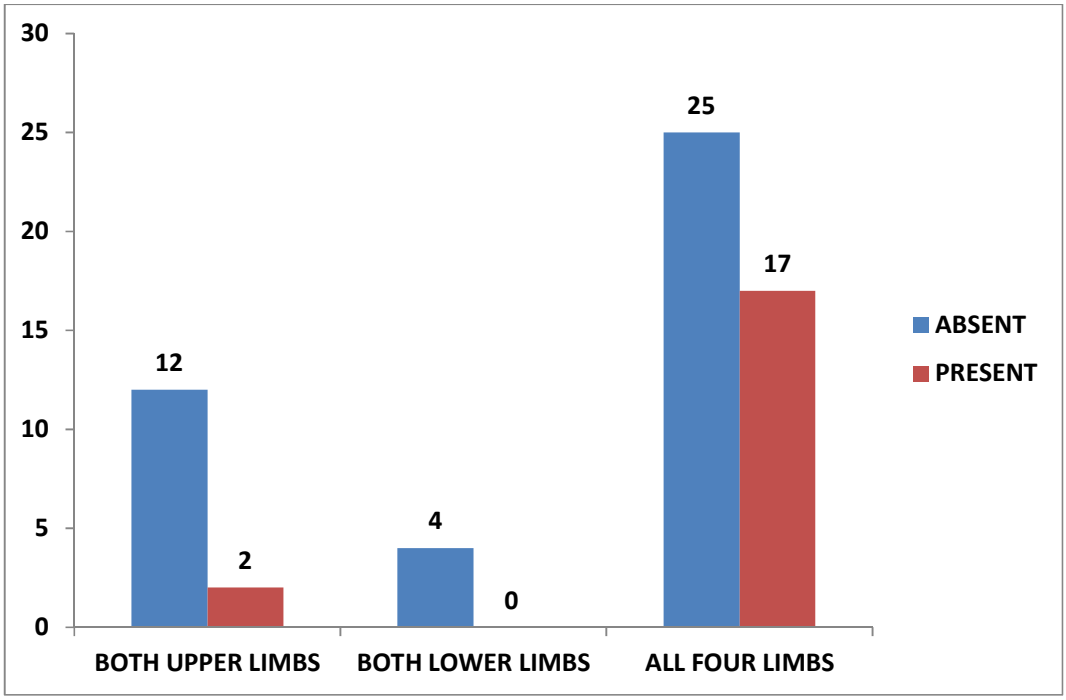
Limbs and microalbuminuria

Out of the 19 patients who had microalbuminuria, 2 patients had involvement of the upper limbs alone, none showed involvement of lower limbs alone, and 17 patients had involvement of both upper limb and lower limb joints. There was no statistically significant association found between any of the groups (p value >0.05).

Table 13: Association between limb invovement and Microalbuminuria

Limbs involved	Number of patients	Microalbuminuria		P value
		Absent	Present	
Both upper limbs	14	12	2	>0.05
Both lower limbs	4	4	0	
All four limbs	42	25	17	
Total	60	41	19	

Figure 11: Association between involvement of limb joints and Microalbuminuria



Morning stiffness and microalbuminuria

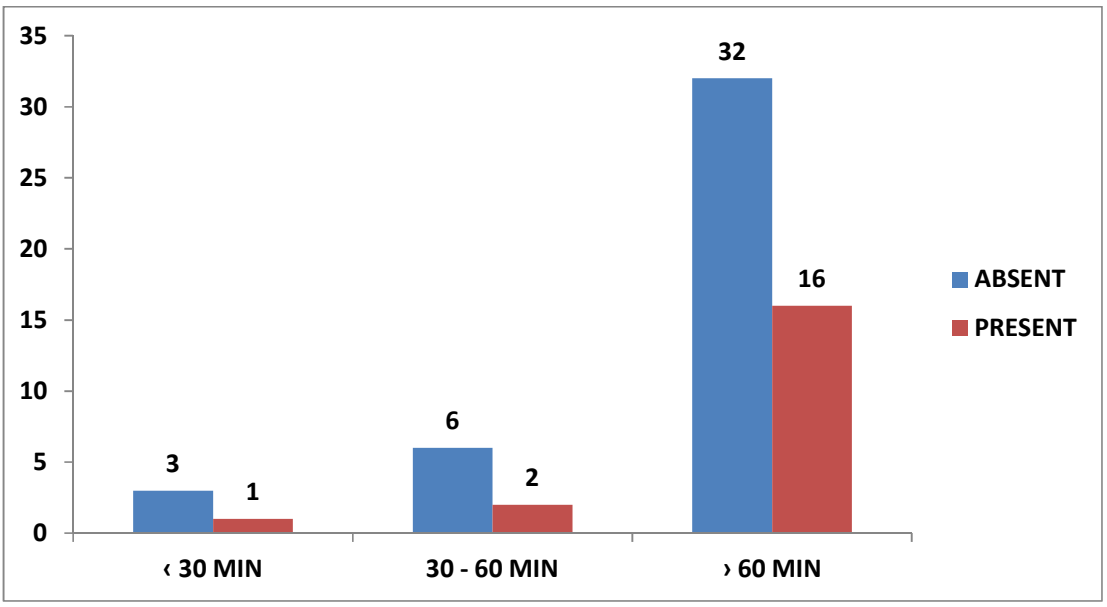
Duration of morning stiffness was found to be lasting for a significantly longer period in those patients having microalbuminuria.

Out of the 19 patients with microalbuminuria, 16 patients had morning stiffness for more than 60minutes, 2 patients had between 30 minutes and 60 minutes, 1patient had morning stiffness lasting less than 30 minutes. But there was no significant association statistically.(The Chi-square value for trend is 0.043 at degree of freedom 1 with p-value of 0.8351).

Table 14: Association between morning stiffness and Microalbuminuria

Duration of morning stiffness	Number of patients	Microalbuminuria		P value
		Absent	Present	
‹ 30 min	4	3	1	0.835
30–60 min	8	6	2	
⩾ 60 min	48	32	16	
Total	60	41	19	

Figure 12: Association between morning stiffness and Microalbuminuria



ESR and microalbuminuria

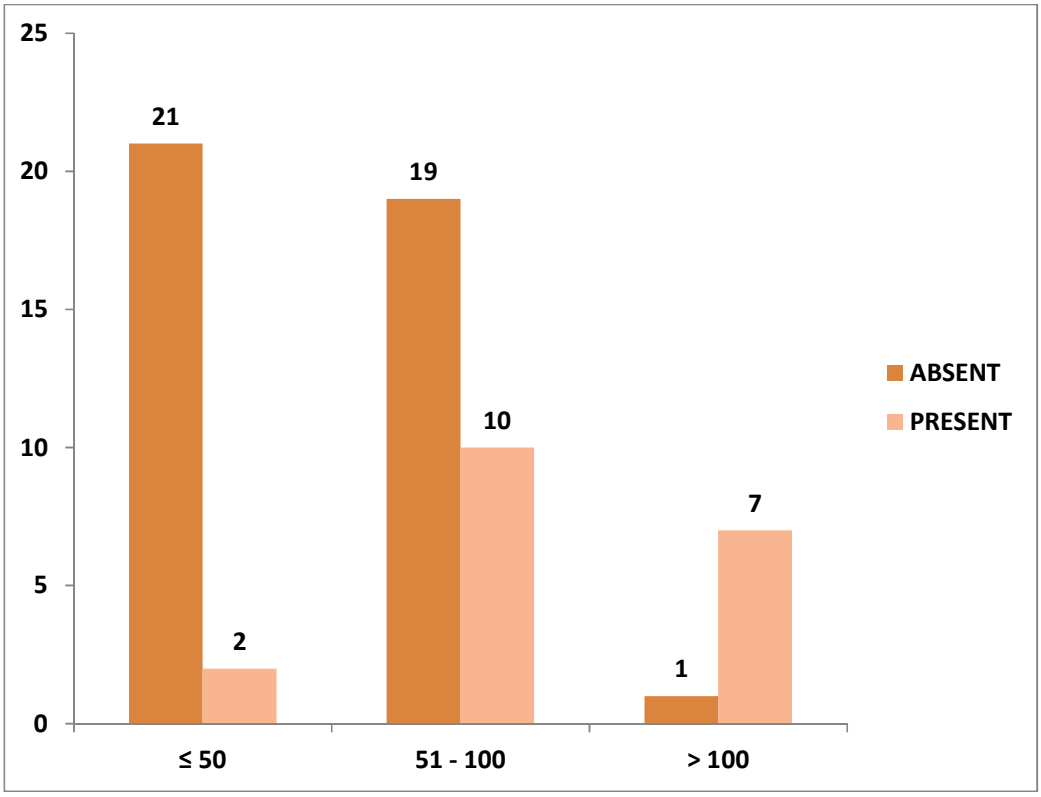
In microalbuminuria positive group, the mean value of ESR was 80.158±26.671, while in microalbuminuria negative group it was 50.122±29.194; this was seen to be statistically significant. Significantly higher values of ESR were observed in patients with positive microalbuminuria. 17 out of the 19 patients with microalbuminuria had ESR values above 50; and 7 had values above 100.

Table 15: Association of ESR with presence of Microalbuminuria

ESR	Number of patients	Microalbuminuria		P value
		Absent	Present	
≤ 50	23	21	2	0.0012
51 –100	29	19	10	
> 100	8	1	7	
Total	60	41	19	

The Chi-square value for trend is 10.488, degree of freedom is 1 and p-value 0.0012.

Figure13: Association between ESR and Microalbuminuria



CRP and microalbuminuria

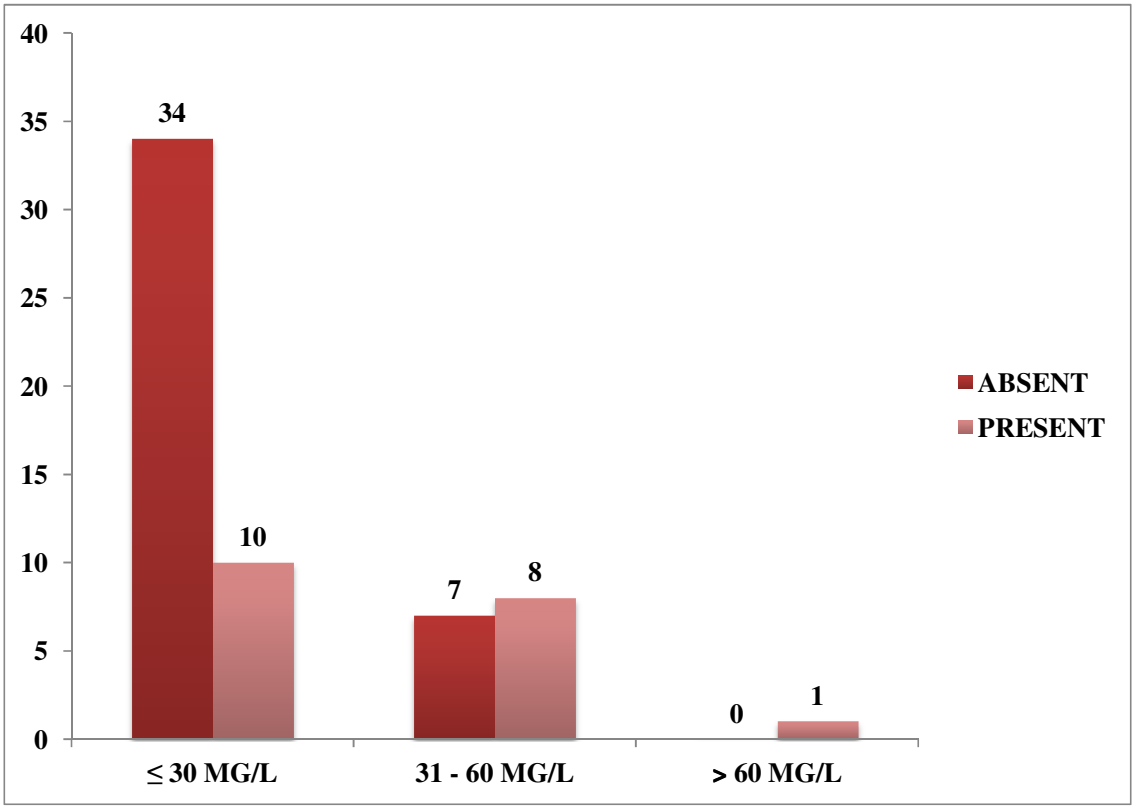
In microalbuminuria positive group, the mean value of CRP was 25.647±22.67 mg/l, while in microalbuminuria negative group it was 17.219±15.366 mg/l.(p-0.0103).Significantly higher values of CRP were observed in patients with positive microalbuminuria.Out of the 19 patients with MA, 16 had positive CRP values. Out of the 19 patients who had microalbuminuria positive, CRP value was ≤ 30 mg/l in 10 patients, between 30 and 60 mg/l in 8 patients, and › 60 mg/l in one patient.

Table 16: Association of CRP with presence of Microalbuminuria

CRP(mg/l)	Number of patients	Microalbuminuria		P value
		Absent	Present	
≤ 30	44	34	10	0.0308
31 –60	15	7	8	
60	1	0	1	
Total	60	41	19	

Chi-square value for trend is 4.664, degree of freedom 1 and p value 0.0308

Figure 14: Association between CRP levels and Microalbuminuria



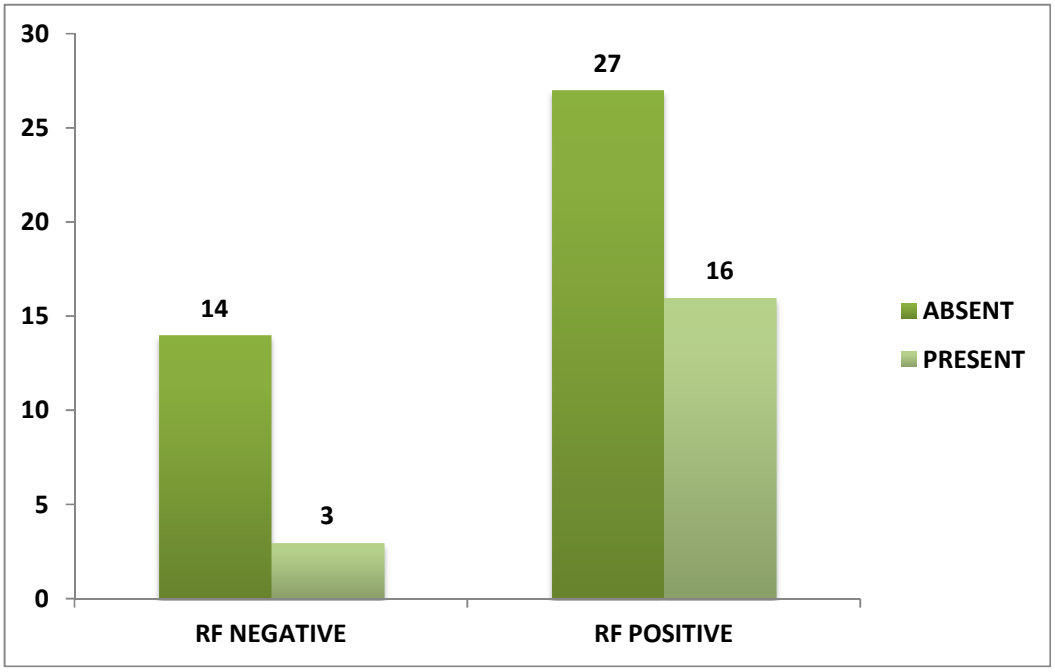
Rheumatoid factor and microalbuminuria

Out of the 19 patients who have microalbuminuria, only 3 were negative for rheumatoid factor. In microalbuminuria positive group, the mean value of RF was 187.947±141.269IU/l, while in microalbuminuria negative group it was 73.627±64.398 IU/l, with a p value of ‹0.0001.

Table 17: Association RA Factor with presence of Microalbuminuria

RA factor	Number of patients	Microalbuminuria	
		Absent	Present
Negative	17	14	3
Positive	43	27	16
Total	60	41	19

Figure 15: Association between RA Factor and Microalbuminuria



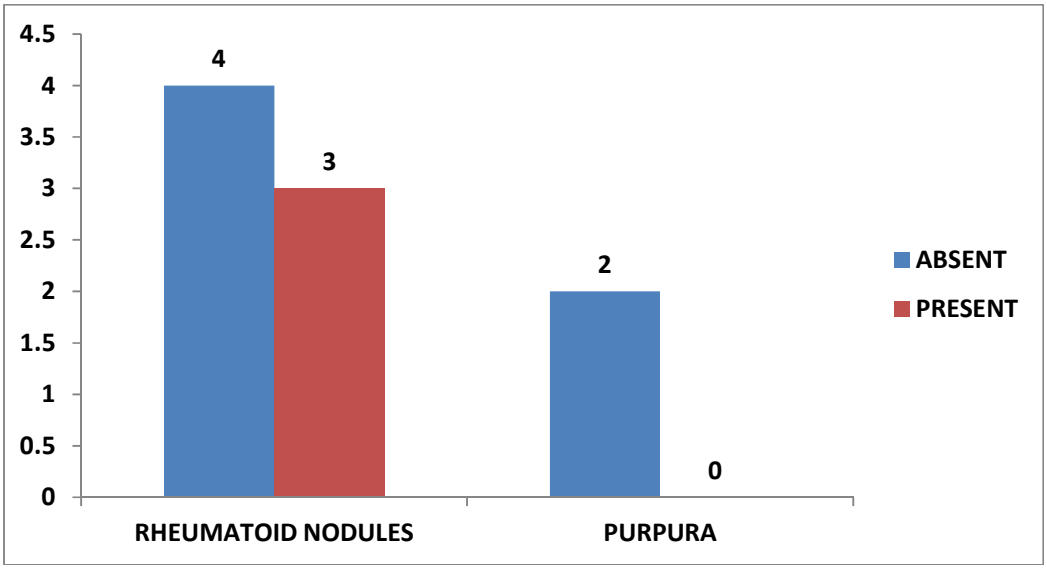
Extra-articular manifestations and microalbuminuria

9 out of the 60 patients who participated in this study showed extra articular manifestations – 7 had rheumatoid nodules and 2 had purpura. Only 3 patients with rheumatoid nodules had microalbuminuria. Patients with purpura did not test positive for microalbuminuria. There was no statistically significant association between microalbuminuria and extra-articular manifestations. Of the 9 patients with extra articular manifestations,8 patients had positive RF.

Table 18: Association of extra-articular manifestations with microalbuminuria

EAM	Number of patients	Microalbuminuria		P value
		Absent	Present	
Rheumatoid nodules	7	4	3	>0.05
Purpura	2	2	0	
Total	9	6	3	

Figure 16: Association of extra-articular manifestations with microalbuminuria



Drugs and microalbuminuria

21out of the 60 (35%) patients who participated in this study were on treatment –7 patients were on NSAIDs alone, 4 patients on NSAIDs+HCQS, one patient was on NSAIDs+HCQS+ STEROID, 6 patients were on NSAIDs+ HCQS+ METHOTREXATE, and3 patients were on NSAIDs+ HCQS+ STEROID+METHOTREXATE. Out of the 21 patients receiving treatment, 10 showed positive microalbuminuria.

Table 19: Association of drugs used with presence of microalbuminuria

Drugs	Number of patients	Microalbuminuria	
		Absent	Present
No or irregular treatment	39	30	9
NSAIDS	7	4	3
NSAIDS + HCQS	4	3	1
NSAIDS + HCQS + STEROID	1	0	1
NSAIDS + HCQS + MTX	6	3	3
NSAIDS + HCQS + STEROID + MTX	3	1	2
Total	60	41	19

DAS 28 and microalbuminuria

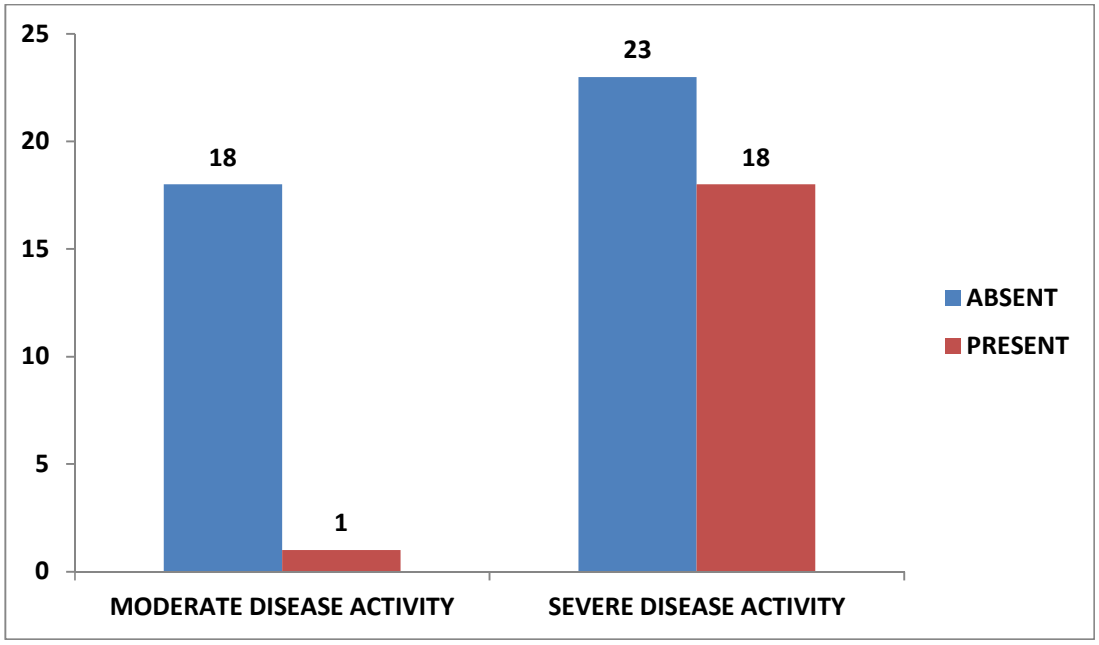
In microalbuminuria positive group, the mean value of DAS28 was 6.73±0.65, while in microalbuminuria negative group it was 5.2±0.63, with a significant p value of 0.003. Of the 19 patients with microalbuminuria, 18 (94.74%) had severe disease activity according to DAS28 score.

Table 20: Association of DAS28 and presence of Microalbuminuria

DAS28	Number of patients	microalbuminuria		P value
		Absent	Present	
Moderate disease activity	19	18	1	0.007
Severe disease activity	41	23	18	
Total	60	41	19	

The Chi-square value for trend is 7.261 with degree of freedom 1 and p-value of0.007

Figure 17: Association of DAS28 and Microalbuminuria



DISCUSSION

This study was done to investigate,

- The prevalence of microalbuminuria inpatients with Rheumatoid Arthritis,
- The relationship between microalbuminuria and disease activity in Rheumatoid Arthritis as assessed by DAS28.

Our study was conducted in Thanjavur Medical College, Thanjavur. Being a tertiary care centre, the patients attending the outpatient department include all those referred from other centres. The average number of patients attending our Rheumatology OPD, on Tuesdays and Thursdays every week, is 100. These include nearly all connective tissue disorders like Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren's syndrome, mixed connective tissue disorders, etc. About 30 patients with Rheumatoid Arthritis attend the OPD daily, out of which 10-20% are new patients attending the clinic for the first time. These patients are either undiagnosed previously or diagnosed and referred from other centres.20-30% patients were our own patients on regular follow up. 30-40% patients were those on irregular follow up. The irregular follow up in majority of them was due to financial difficulties. The Rheumatoid Arthritis patients in our study were seen to have either moderate or severe disease activity as defined by DAS28 score. This may possibly be due to the reason that this institution being a tertiary health

care level will have only referred cases. The duration of symptoms in every one of them was less than five years.

In the present study, the mean age of the population was 44.55 years. Maximum number of patients was in the 41-50 age groups. The mean value for age in both microalbuminuria positive and negative group was similar, 48.32±14.18 and 42.81±13.39 respectively. The mean value for age in females was 43.77yrs(SD-14.128) whereas in males it was 46.53 yrs (SD-13.005). This is according to the observation by Akil M et al[12]that occurrence of Rheumatoid Arthritis is highest in the forties.

In the present study, age was not a significant factor for MA (P-0.151).Pederson L M et al also got similar results.[100]

Among the participants in this study, there were 43females (71.7%) and 17males (28.3%), with a female to male ratio of 2.53. This is a bit lower than the usually observed ratio of 3:1.

The mean duration of symptoms among Rheumatoid Arthritis patients in this study was 17.88 months. Most of the patients (35%) had symptom duration ranging between 11-20 months. 80% of the patients gave a definite history of morning stiffness of more than 1 hour duration. 70% patients had constitutional symptoms. Rheumatoid nodules were present in 11.67% of patients. Joint deformity and purpura were observed in 11.7% and 3.3% of patients respectively.

A total of 4 to 28 joints were involved in patients with rheumatoid arthritis with the mean value for tender joints being 11.2±6.671 and swollen joints being 13.067±6.362. 71.7% of patients had 4 – 15 painful joints and 66.4% patients had edema of 4 – 15 joints.

In this study, 19 patients (31.67%) had microalbuminuria out of which 12 were females and 7 were males. There was no significant difference in sex distribution between microalbuminuria positive and negative groups (p-0.365).In the study by Pederson L M et al, they observed that there is no difference in the median ratio of albumin excretion between males and females in Rheumatoid Arthritis patients (p-0.1).[100] Similar observation was made by Monica Verma et al[105] also.

We observed that out of the 19 patients with positive microalbuminuria, 18 patients showed presence of constitutional symptoms like anorexia, fever and tiredness (p-0.0054). In our study, out of the 19 patients having microalbuminuria, 16 (84.2%) patients had morning stiffness lasting more than one hour; but there was no significant statistical association between morning stiffness and microalbuminuria. From the currently obtained data, it suggests that microalbuminuria is an indicator of severe disease activity.

9 patients in our study had extra articular manifestations in the form of purpura (2) and rheumatoid nodules (7). Rheumatoid nodules was found to be the most common extra articular manifestation in this study, similar to the

observations made in the studies by Turesson[115] et al. Tests for detecting microalbuminuria was positive only in 3 patients with rheumatoid nodules and none with purpura. No significant statistical association was found between MA and EAM. In view of the fact that the majority of the patients were having shorter disease duration, it is difficult to comment about the relationship between microalbuminuria and EAM. 8 out of the 9 patients with EAM had positive RF. This is also according to the studies by Turesson [114] et al.

The prevalence of microalbuminuria in Rheumatoid Arthritis was found to be 31.7% in our study. This was similar to the findings obtained in other studies including Pederson L M et al and Bhatt G et al.According to Pederson L M et al [100], the prevalence of microalbuminuria in Rheumatoid Arthritis was 27.7%. Bhatt G etal[101]observed the prevalence of microalbuminuria to be 30%. In the studies by Monica Verma et al[105], the relative occurrence of microalbuminuria in Rheumatoid Arthritis patients was 26%.

In our study, there were no age and sex matched controls since this was not a case control study. However in the study conducted by Pederson L M et al[100]and Bhatt G et al[101], the prevalence of microalbuminuria was significantly more in Rheumatoid Arthritis cases 27.7% v/s 7.8% in age and sex matched controls and 30% as compared to 5% in age and sex matched controls, respectively. According to Monica Verma et al[105], the relative

incidence of microalbuminuria in rheumatoid arthritis patients was 26% as against 4% in controls.

Saito M et al compared the urinary albumin indices in patients having Rheumatoid Arthritis ,osteoarthritis and normal control subjects and observed that the urinary albumin indices were 25.7+/-38.2, 11.4+/-11.5 and 7.7+/-3.5 respectively, significantly greater in patients with Rheumatoid Arthritis.[102]

Sihvonen et al in 2004 saw that microalbuminuria was present in 34 out of 600 Rheumatoid Arthritis patients and 27 out of 470 controls. Rheumatoid Arthritis patients with microalbuminuria were seen to have higher mortality rate when compared with those patients without MA, with a hazard ratio of 2.77 in MA positive patients.[28] These observations suggests that microalbuminuria is comparatively common in patients with Rheumatoid Arthritis.

In inflammatory diseases, there seems to be increased systemic vascular permeability to plasma proteins. Hence, excretion of microalbumin in urine is indicative of a systemic response in cases of an acute phase reaction [101]. The increased rate of albumin excretion in RA can either be due to its inflammatory effect on vascular permeability or due to the side effects caused by the nephrotoxic drugs used for the disease therapy. Renal complications are more in Rheumatoid Arthritis patients,[3031] and higher mortality is observed in the presence of proteinuria.[32]So, it is essential to have a sensitive method for reliable clinical measurement of dysfunction of the

kidneys. The present study confirms the occurrence of pathological albuminuria in several RA patients without any history suggestive of renal dysfunction, diabetes or hypertension. This is consistent with the earlier reports regarding subclinical renal dysfunction in RA. [17]

The reversible subclinical stage of renal disease may stay unnoticed for a long duration, and it's necessary to detect it at the earliest[31]. The usual measures used for measuring kidney function like urine total protein assays, urine dipstick testing, urine cytology and serum creatinine may not identify mild to moderate damages to the kidneys. Every patient having microalbuminuria in this study showed normal levels of serum creatinine, macroalbuminuria was absent and also showed normal 24 hour urine protein. Estimation of urine albumin levels by immunoturbidimetry or other immunochemical methods is a simple and sensitive method for identifying early subclinical damage to the kidneys. [29]

RA patients in this study belonged either to the moderate or severe disease activity group categorised according to the DAS28 score. This may be due to the reason that being a tertiary care centre, more of referred cases are seen here.

In this study, it was found that there is significant association between ESR and MA. In microalbuminuria positive group, the mean value of ESR was 80.158±26.671, while in microalbuminuria negative group it was 50.122±29.194 (p-0.0003). 17 out of the 19 patients (89.47%) with

microalbuminuria had ESR values above 50; and 7 (36.84%) had values above 100. Results in our study showed that MA increases with increasing ESR levels. According to Monica Verma et al[105], there is significant relationship between MA and ESR ($p < 0.001$). Pederson L M et al observed no statistically significant association between ESR and MA in patients with Rheumatoid Arthritis, even though elevated ESR levels were observed in patients having microalbuminuria. This could be partly due to the reason that some patients with normal urine albumin levels showed elevated ESR levels for causes other than rheumatoid arthritis. Another explanation given by them was that majority of the patients in the study were already on treatment with DMARDs [100].

In our study, the mean value for CRP was 25.65±22.67in MA positive patients

when compared to 17.22±15.37 in MA negative patients(p-0.0301). Significantly elevated levels of CRP were observed in patients having MA. Out of the 19 patients with MA, 16(84.2%) showed positive CRP results. Of the 19 patients with microalbuminuria, CRP value was ≤ 30 mg/l in 10 patients, between 30 and 60 mg/l in 8 patients, and › 60 mg/l in one patient.

In our study, it was found that levels of microalbuminuria increases as the CRP levels increase suggesting a direct association between the two. As elevated ESR and CRP are markers of severe disease, microalbuminuria also suggests a severe disease. In the study by Nakamura et al[103], CRP levels

representing low grade inflammation was found to be significantly associated with microalbuminuria. Pederson L M et al[100]also got similar results and observed that the median values (ranges between) were 112 (16-1615) nmol/l for CRP and also that CRP was significantly associated with UACR. Significant relationship between MA and CRP was also noted by Bhatt G et al[101], and Moniva Verma et al[105].

In this study, only 3(15.79%) patients in MA positive group had RA factor negative, while 16(84.21%) had positive RF. In microalbuminuria positive group, the mean value of RF was 187.947±141.269IU/l, while in microalbuminuria negative group it was 73.627±64.398 IU/l, with a p value of ‹ 0.0001.

A significant association was observed between RA factor and microalbuminuria in our study. Similar results were also obtained by Gordon et al[58], Turesson et al[5960] and Young et al[61], and found that RA factor was generally absent in patients with milder disease. This indicates that microalbuminuria is related with severe disease activity.

According to this study, the mean value for swollen joints was 15.89±5.64 in microalbuminuria positive group when compared with 11.76±6.31 in microalbuminuria negative group (P-0.018), and the mean value for tender joints was 14.32±6.64 in microalbuminuria positive group when compared with 9.76±6.25 in microalbuminuria negative group(p-0.0125). These results suggest that microalbuminuria is significantly

associated with disease activity in RA. Similar number of joints was involved in the study by Monica Verma et al[105](p< 0.05,). However in this study, no significant relationship was found between occurrence of microalbuminuria and the limb involved (upper or lower limb or both).

In this study, it was observed that the mean duration of symptoms was significantly more in MA positive group (24.68±12.06) than MA negative group with a p value of 0.0004. Same results are obtained by statistical analysis suggesting that microalbuminuria increases with increase in disease duration. Hence, patients having symptoms for a longer period are more prone to have microalbuminuria.

In the study by Pederson L M et al[100], results indicate that patients having microalbuminuria had significantly longer median disease duration than the group with normal UACR. Similar results were also in the studies by Bhatt G et al[101] and Monica Verma et al [105].

The relationship between MA and disease duration may be either due to severe and chronic disease affecting the kidneys increasing the permeability of systemic vessels, or due to the additional nephrotoxic therapy given to the patients having severe chronic disease.

Our study showed significant association between MA and DAS28 score. The mean DAS28 score was 6.73±0.65 in microalbuminuria positive group when compared with 5.2±0.63 in microalbuminuria negative group (p‹0.0001). Out of the 19 patients having microalbuminuria, 18 (94.74%) had

severe disease activity. There was statistically significant association between MA and DAS28 score with a p value of 0.007. The mean value for MA was found to be 34.47±45.35 in the moderate disease activity group and 94.39±91.48 in the severe disease activity group. This difference was also observed to be statistically significant with a p value 0.009. Observations made by Harkrishnan Aggarval et al[111]and V Raveendran et al[112] were also similar.

In our study, we got statistically significant association between drug therapy and the presence of MA .Out of the 19 patients with MA, 10 were on treatment with DMARDs or NSAIDs or both. In the study by Pederson L M [100], MA was found to be significantly more in patients treated with gold and pencillamine. Also in the study by Bhatt G [101] et al, treatment with NSAIDs, methotrexate, salazopyrene, chloroquine and steroids was found to be significant. However, these patients have severe disease activity and longer duration of disease.

The mean values for DAS28 score, CRP, ESR and RF were higher in the patients having microalbuminuria than those who do not have. Moreover, the number of swollen/tender joints, and duration of symptoms were found to be more in patients with MA. MA was noted to be significantly associated with these parameters. Since ESR, CRP, and DAS28 are considered as indicators of disease activity, presence of MA indicates a severe disease.

Microalbuminuria and subclinical damage to the kidneys are more common in RA especially in those having greater disease duration. Routine investigations like serum creatinine may not be helpful in identifying subclinical damage to kidneys[100]. Since microalbuminuria is a good predictor of kidney dysfunction, our study shows that subclinical renal disease is frequently observed in Rheumatoid Arthritis patients. Still, the long term prognosis for renal involvement in rheumatoid arthritis patients needs to be clarified by means of longitudinal studies. We think that in most of the patients having microalbuminuria in RA, renal involvement is reversible and the chances of developing end stage renal disease is scarce if timely intervention done.

CONCLUSIONS

About one third of the patients having rheumatoid arthritis is seen to have microalbuminuria.

In this study microalbuminuria was found to be significantly associated with disease activity in rheumatoid arthritis as assessed by DAS28, ESR, CRP and RA Factor. Microalbuminuria is also found to be associated with duration of disease and presence of active symptoms. There was no significant association between gender, age and drugs with microalbuminuria.

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ANNEXURE 1

Proforma for the study on prevalence of microalbuminuria in rheumatoid arthritis and its association with disease activity

PATIENT PROFILE

Name Age(in years) Sex-male/female

Occupation

Address

Phone no

Op no Date

Presenting Complaints

1.Pain in small joints of hand

Present/absent

Unilateral/bilateral

Duration(months)☐

2.Morning stiffness

<30 min ☐30-60 min ☐>60 min ☐

3.Constitutional symptoms

fever☐anorexia ☐tiredness ☐

4.Pain in other joints

UPPER LIMB☐LOWER LIMB☐ BOTH ☐

5. Other joints involved(if any) ☐Duration(months)☐

6. Deformities – present/absent

If present, duration (in months)☐

Past history

Family history - Rheumatoid Arthritis☐Hypertension☐Diabetes☐

Personal history

Diet-veg☐nonveg☐mixed☐

Appetite-normal☐increased☐decreased☐

Sleep- normal☐increased☐decreased☐

Bowel

Bladder

Smoking-yes☐no☐

Alcohol-yes☐no☐

Treatment history

GENERAL EXAMINATION

Built-poor ☐moderate ☐well☐

Nourishment-poor ☐moderate ☐well ☐

Pallor-yes ☐no ☐

Icterus-yes ☐no ☐

Cyanosis-yes ☐ no☐

Clubbing-yes ☐ no☐

Lymphadenopathy –yes ☐ no☐

Edema –yes ☐ no☐

Oral cavity

height(cm) weight(kg)

pulse BPJVPyes ☐no ☐

Temp RR

Rheumatoid nodules☐Otherextra articular manifestations☐

LOCAL EXAMINATION

Deformities – yes ☐no ☐

Restriction – yes ☐no ☐

SYSTEMIC EXAMINATION

Cardiovascular system

Inspection

Palpation

Percussion

Auscultation

Respiratory System

Inspection

Palpation

Percussion

Auscultation

Gastrointestinal Tract

Inspection

Palpation

Percussion

Auscultation

Central Nervous System

HMF

Speech

Cranial nerves

Motor system

Sensory system

Reflexes -superficial

- deep

INVESTIGATIONS

- Blood Routine Examination
- Urine Routine Examination
- Blood urea
- Serum creatinine
- Chest X-ray
- ECG
- CRP
- RA factor
- RBS
- Urine p/c
- 24 hour urine protein
- DAS28 score
- VAS score (mm)

CONSENT FORM

I _____ hereby give consent to participate in the study conducted on prevalence of microalbuminuria in Rheumatoid arthritis and its relation with disease activity in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant

INFORMATION SHEET

We are conducting a cross sectional study on **a study of prevalence of microalbuminuria in rheumatoid arthritis and its association with disease activity** in the Department of General Medicine, Thanjavur medical college and hospital, Thanjavur – 613004.

At the time of announcing the results and suggestions, name and identity of the patient will be confidential.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator signature of participant

Date:

KEY TO THE MASTER CHART

- **OP**-out patient number
- **Duration**-duration of symptoms in months
- **TJ** –number of tender joints involved
- **SJ**-number of swollen joints involved
- **Limb**-limbs involved- **QL**-all four limbs, **BUL**-both upper limbs only, **BLL**-both lower limbs only
- **Morning stiffness**-duration of morning stiffness in hour
- **Constitutional symptoms**-**0**-absent, **1**-present
- **Treatment** – drugs taken by patients, **N**-no/irregular treatment, **NSAID**-nonsteroidal anti-inflammatory drugs, **MTX**-methotrexate, **HCQS**-hydroxychloroquin,**STEROID**-steroid
- **DJ**-joint deformity- **1**- present, **0**-absent
- **EAM**-extraarticular manifestations-**RN**-rheumatoid nodules, **P**-purpura
- **VAS**-visual analogue scale score in millimeters
- **ESR**-erythrocyte sedimentation rate in centimeters/hour
- **CRP**-C-reactive protein in milligram/litre
- **U.ACR**-urine albumin-creatinine ratio in microgram per milligram
- **RF**- rheumatoid factor in international units/deciliter
- **DAS28**-disease activity score
- **B.Ur**-blood urea in mg/dl
- **S.Cr**.-serum creatinine in mg/dl

MASTER CHART

name	Sex	Age	OP	Duration	TJ	SJ	Limb	Morning stiffness	constitutional symptoms	Treatment	DJ	EAM	VAS	ESR	CRP	RF	U. ACR	DAS28	B. Ur	S. Cr
Anjamma	F	55	102818	8	4	8	QL	› 1	1	N	0	0	75	8	18	15	29	5.62	33	1
Jagadhambal	F	50	152290	22	16	18	QL	› 1	1	N	0	RN	60	67	45	100	158	6.93	24	1
Uthayarai	F	43	151407	18	20	22	QL	› 1	1	NSAIDs	0	0	82	90	49	36.5	21	5.79	33	0.9
Arumugam	M	64	135323	7	4	4	QL	‹ 0.5	0	N	0	0	66	10	3	23	18	5.41	36	0.8
Vlarmathi	F	48	152361	12	14	16	QL	› 1	1	N	0	0	54	10	5	15	28	5.55	37	0.9
Anjalaidevi	F	54	151904	24	14	14	QL	› 1	1	NSAIDs + HCQS	0	0	50	55	15	30	288	6.71	32	0.8
Sutha	F	50	6171	14	16	18	QL	› 1	1	NSAIDs + HCQS +MTX	0	0	68	9	6	20	19	5.51	24	0.7
Povinammal	F	20	152423	24	18	24	BUL	› 1	0	N	0	0	88	45	2	60	27	6.22	25	0.8
Jayanthi	F	55	144502	10	12	16	QL	› 1	1	NSAIDs	1	0	80	40	7.7	140	22	4.15	24	0.7
Sekar	M	38	150642	12	6	8	QL	› 1	1	N	0	0	74	42	4.9	61	25	5.61	22	0.8
Rajenthiran	M	44	1062	6	8	12	BLL	› 1	1	N	0	P	52	91	4	40	27	4.36	34	0.6
Manikyanagam	M	43	81852	24	16	18	QL	› 1	0	N	0	0	90	110	13	440	123	6.37	35	0.9
Kumutha	F	58	58029	4	4	4	BUL	› 1	1	N	0	0	85	64	2.6	175	29	4.95	33	0.9
Papa	F	60	6671	26	28	28	QL	‹ 0.5	1	NSAIDs	0	RN	71	61	33	255	221	4.95	36	0.8
Thiyagaran	M	31	157316	24	26	28	QL	.5 – 1	0	N	0	0	78	67	33	96	18	4.97	34	0.9
Anushiya	F	53	155283	6	8	12	QL	.5 – 1	0	NSAIDs + HCQS +MTX	1	0	52	60	27	102	23	4.87	34	0.9
Saniyamal	F	72	157725	22	8	10	QL	› 1	1	N	0	0	69	50	14.8	27	129	6.47	33	0.7
Maheshwari	F	27	11435	16	12	14	BUL	› 1	1	N	0	0	85	16	38	30	27	5.04	32	0.7
Sumathi	F	31	173160	18	12	14	QL	› 1	1	NSAIDs + HCQS	0	0	77	30	5.9	51	17	4.53	25	0.8
Indhra	F	62	173114	3	4	4	QL	› 1	1	N	0	0	59	95	54	40	29	4.34	26	0.8
Saithabeevi	F	48	156771	21	20	22	QL	› 1	1	NSAIDs + HCQS +MTX	0	RN	64	105	14	353	212	6.81	33	1.1
Venu	M	44	1728301	13	12	14	BLL	› 1	0	N	1	0	61	48	11	59	16	5.54	35	1.1
Chithra	F	36	163162	34	22	24	BUL	› 1	1	N	0	0	90	100	5	40	29	5.92	25	0.9
Thangavel	M	42	67206	33	20	20	QL	› 1	1	NSAIDs + HCQS + STEROID	0	0	46	62	54	152	222	6.22	37	1
Subhramanyan	M	24	66993	7	4	6	BUL	› 1	1	N	0	0	58	121	5	440	150	6.1	33	1
Annailakshmi	F	72	152151	6	4	6	QL	› 1	0	N	0	0	65	40	8	31	11	6.37	35	1
Periyanayaki	F	43	54312	8	6	8	BUL	› 1	1	N	0	RN	72	65	2.8	175	29	4.87	37	1.1

Aishabeevi	*F*	*29*	*195313*	*9*	*6*	*8*	*QL*	*› 1*	*1*	*N*	*0*	*0*	*35*	*55*	*49*	*175*	*129*	*7.37*	*32*	*1.1*
Selvamani	*M*	*49*	*295*	*9*	*6*	*8*	*QL*	*.5 – 1*	*1*	*N*	*0*	*0*	*44*	*90*	*50*	*90*	*28*	*5.45*	*31*	*0.9*
Lakshmimaniyal	*F*	*39*	*150624*	*9*	*8*	*8*	*BUL*	*› 1*	*0*	*NSAIDs + HCQS + STEROID+MTX*	*0*	*0*	*76*	*10*	*3.8*	*34*	*25*	*5.38*	*31*	*0.9*
Latheef	*M*	*50*	*98651*	*9*	*4*	*6*	*QL*	*› 1*	*1*	*N*	*0*	*P*	*52*	*60*	*21*	*125*	*27*	*5.07*	*30*	*0.8*
Nagavali	*F*	*62*	*444*	*16*	*8*	*8*	*QL*	*› 1*	*1*	*N*	*1*	*0*	*38*	*106*	*39*	*191*	*23*	*5.06*	*35*	*0.8*
Chellama	*F*	*14*	*178967*	*14*	*8*	*8*	*BLL*	*.5 – 1*	*0*	*NSAIDs + HCQS*	*0*	*0*	*65*	*30*	*5.8*	*23*	*26*	*5.51*	*30*	*0.6*
Ambika	*F*	*34*	*190057*	*30*	*22*	*24*	*BUL*	*› 1*	*1*	*N*	*0*	*0*	*60*	*100*	*1*	*55*	*22*	*5.31*	*34*	*0.6*
Nazeerahammed	*M*	*44*	*200572*	*10*	*4*	*8*	*QL*	*‹ 0.5*	*1*	*N*	*0*	*0*	*83*	*45*	*4*	*35*	*27*	*5.55*	*33*	*0.8*
Tamil Selvi	*F*	*49*	*33614*	*13*	*12*	*16*	*QL*	*› 1*	*1*	*N*	*0*	*0*	*48*	*80*	*6*	*190*	*109*	*7.59*	*31*	*0.8*
Mllika	*F*	*24*	*05756*	*14*	*6*	*8*	*BUL*	*› 1*	*0*	*N*	*0*	*0*	*58*	*82*	*19*	*53*	*23*	*5.41*	*36*	*0.7*
Devika	*F*	*33*	*156822*	*13*	*4*	*6*	*QL*	*› 1*	*1*	*NSAIDs + HCQS +MTX*	*0*	*0*	*56*	*20*	*3.46*	*153*	*21*	*5.79*	*40*	*0.9*
Manokar	*M*	*43*	*126765*	*31*	*16*	*16*	*QL*	*› 1*	*1*	*NSAIDs*	*0*	*0*	*64*	*103*	*7.7*	*20*	*134*	*6.33*	*34*	*0.7*
Ramayaan	*M*	*38*	*160544*	*22*	*12*	*14*	*QL*	*.5 – 1*	*1*	*NSAIDs*	*0*	*0*	*76*	*60*	*70*	*125*	*151*	*6.32*	*35*	*0.9*
Fathimabhanu	*F*	*42*	*30755*	*21*	*8*	*14*	*QL*	*› 1*	*1*	*NSAIDs + HCQS +MTX*	*0*	*0*	*85*	*34*	*31*	*380*	*189*	*7.32*	*33*	*0.9*
Aathimulam	*M*	*81*	*10376*	*36*	*20*	*20*	*QL*	*› 1*	*1*	*NSAIDs + HCQS + STEROID+ MTX*	*0*	*0*	*88*	*65*	*5.9*	*121*	*263*	*7.65*	*36*	*1.1*
Vijaya	*F*	*49*	*173384*	*10*	*4*	*12*	*QL*	*.5 – 1*	*0*	*N*	*0*	*RN*	*76*	*46*	*8.9*	*64*	*20*	*4.67*	*34*	*0.8*
Priya	*F*	*27*	*234032*	*10*	*6*	*8*	*BLL*	*› 1*	*0*	*N*	*1*	*0*	*70*	*34*	*5.8*	*35*	*30*	*4.87*	*35*	*0.7*
Sawndharya	*F*	*50*	*233920*	*60*	*28*	*26*	*QL*	*› 1*	*1*	*NSAIDs + HCQS + STEROID+MTX*	*0*	*0*	*60*	*110*	*50*	*130*	*278*	*6.47*	*32*	*0.7*
Shahunthala	*F*	*39*	*195970*	*12*	*10*	*14*	*QL*	*› 1*	*1*	*NSAIDs + HCQS +MTX*	*0*	*0*	*47*	*70*	*0.4*	*359*	*297*	*6.76*	*33*	*0.6*
Kavitha	*F*	*50*	*235633*	*13*	*4*	*8*	*BUL*	*› 1*	*0*	*N*	*0*	*0*	*54*	*10*	*3*	*28*	*23*	*5.04*	*32*	*0.9*
Balu	*M*	*43*	*238986*	*14*	*4*	*6*	*QL*	*› 1*	*1*	*N*	*0*	*0*	*78*	*70*	*18.5*	*50*	*27*	*4.36*	*24*	*1*
Vijayakumar	*M*	*53*	*112662*	*16*	*6*	*8*	*QL*	*› 1*	*1*	*N*	*1*	*RN*	*83*	*15*	*4*	*24*	*28*	*5.61*	*25*	*0.9*
Ilanjiyan	*F*	*41*	*105775*	*14*	*8*	*14*	*BUL*	*› 1*	*1*	*NSAIDs + HCQS*	*0*	*0*	*65*	*62*	*18*	*330*	*23*	*4.15*	*24*	*0.9*
Pushpalatha	*F*	*36*	*290*	*30*	*16*	*16*	*QL*	*‹ 0.5*	*0*	*N*	*0*	*0*	*50*	*21*	*5*	*18.2*	*26*	*6.3*	*22*	*0.8*
Vidhyalekshmi	*F*	*51*	*147633*	*11*	*8*	*8*	*QL*	*› 1*	*0*	*N*	*1*	*0*	*58*	*25*	*36*	*26*	*22*	*3.26*	*26*	*0.6*
Dhanalakshmi	*F*	*32*	*59300*	*18*	*12*	*14*	*BUL*	*› 1*	*1*	*N*	*0*	*0*	*86*	*120*	*39*	*150*	*101*	*6.75*	*34*	*0.6*
Saraswathi	*F*	*23*	*11192*	*34*	*18*	*14*	*BUL*	*› 1*	*1*	*NSAIDs*	*0*	*0*	*81*	*60*	*25*	*160*	*18*	*4.93*	*35*	*0.7*
Amutha	*F*	*43*	*20348*	*32*	*20*	*20*	*QL*	*› 1*	*0*	*N*	*0*	*0*	*68*	*65*	*3*	*121*	*29*	*5.31*	*30*	*0.8*
Kalavathidevi	*F*	*17*	*210473*	*22*	*14*	*16*	*BUL*	*.5 – 1*	*0*	*NSAIDs*	*0*	*0*	*45*	*55*	*5*	*50*	*17*	*5.55*	*34*	*1*
Ravathi	*F*	*53*	*146174*	*15*	*6*	*8*	*QL*	*› 1*	*1*	*N*	*0*	*0*	*66*	*54*	*14.8*	*59*	*18*	*5.41*	*33*	*1.1*
Selvapani	*F*	*57*	*168949*	*32*	*10*	*12*	*QL*	*.5 – 1*	*1*	*N*	*0*	*0*	*72*	*105*	*53*	*39*	*177*	*7.08*	*32*	*1.1*
Kaliyamoorthy	*M*	*60*	*174916*	*36*	*12*	*12*	*QL*	*› 1*	*1*	*N*	*0*	*0*	*55*	*90*	*11.5*	*85*	*222*	*7.59*	*35*	*0.9*
Nandhini	*F*	*59*	*205039*	*16*	*4*	*4*	*QL*	*› 1*	*0*	*N*	*0*	*RN*	*65*	*65*	*19*	*85*	*25*	*5.61*	*25*	*0.8*